EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4992	IL-11 or interleukin adj "11"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2007/02/19 15:46
L2	1460	soluble same receptor same (bone or osteoporosis or paget$ or myeloma)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 15:46
L3	292	1 and 2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 15:46
L4	99	1 same 2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 15:47

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	603	IL-11 same bone	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2007/02/19 15:38
L2	12252	binding adj peptide	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 15:38
L3	71	1 and 2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 15:38

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2153	(shaughnessy.in. or austin.in.) and (interleukin or IL-11)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 14:27
L2	86	(shaughnessy.in. or austin.in.) and (IL-11)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 14:28
L3	9	(shaughnessy.in. or austin.in.) not gurney.in. and (IL-11)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/02/19 14:28

```
Welcome to DIALOG

Dialog level 05.16.01D
? b 411;set files biotech
     19feb07 15:40:05 User219511 Session D676.2
        $0.00   0.117 DialUnits File410
    $0.00  Estimated cost File410
    $0.02  TELNET
    $0.02  Estimated cost this search
    $0.48  Estimated total session cost   0.249 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2007 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 26 files in your file list.
  (To see banners, use SHOW FILES command)
? s IL-11 and bone and binding and peptide?

Your SELECT statement is:
  s IL-11 and bone and binding and peptide?

       Items  File
       -----  ----
           1  5: Biosis Previews(R)_1969-2007/Feb W2

  1 file has one or more items; file list includes 26 files.

? s IL-11 and bone and ((binding and peptide?) or (soluble and receptor?)

Your SELECT statement is:
  s IL-11 and bone and ((binding and peptide?) or (soluble and receptor?)

       Items  File
       -----  ----
>>>Unmatched parentheses
? s IL-11 and bone and ((binding and peptide?) or (soluble and receptor?))

Your SELECT statement is:
  s IL-11 and bone and ((binding and peptide?) or (soluble and receptor?))

       Items  File
       -----  ----
           3  5: Biosis Previews(R)_1969-2007/Feb W2
           3  34: SciSearch(R) Cited Ref Sci_1990-2007/Feb W2

  2 files have one or more items; file list includes 26 files.

? s (IL-11 or (interleukin (w) 11)) and bone and ((binding and peptide?) or (soluble and receptor?))

Your SELECT statement is:
  s (IL-11 or (interleukin (w) 11)) and bone and ((binding and peptide?)
or (soluble and receptor?))

       Items  File
       -----  ----
          25  5: Biosis Previews(R)_1969-2007/Feb W2
           6  24: CSA Life Sciences Abstracts_1966-2007/Nov
          24  34: SciSearch(R) Cited Ref Sci_1990-2007/Feb W2
           4  45: EMCare_2007/Feb W2
           6  71: ELSEVIER BIOBASE_1994-2007/Feb W3
          32  73: EMBASE_1974-2007/Feb 19
           2  94: JICST-EPlus_1985-2007/Feb W3
           1  135: NewsRx Weekly Reports_1995-2007/Feb W2
           1  144: Pascal_1973-2007/Feb W2
          13  155: MEDLINE(R)_1950-2007/Feb 16
          21  357: Derwent Biotech Res.__1982-2007/Feb W2
          30  399: CA SEARCH(R)_1967-2007/UD=14609

  12 files have one or more items; file list includes 26 files.

? save temp; b 155,5,34,71,73,357;exs;rd
Temp SearchSave "TE379272373" stored
     19feb07 15:43:52 User219511 Session D676.3
        $10.88   3.700 DialUnits File411
    $10.88  Estimated cost File411
     $1.06  TELNET
    $11.94  Estimated cost this search
    $12.42  Estimated total session cost   3.949 DialUnits

SYSTEM:OS - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2007/Feb 16
       (c) format only 2007 Dialog
*File 155: MEDLINE has resumed updating with UD20061209. Please
see HELP NEWS 154 for details.
  File   5:Biosis Previews(R) 1969-2007/Feb W2
       (c) 2007 The Thomson Corporation
*File   5: In preparation for coming enhancements, accession numbers will
change soon. See HELP NEWS 5 for details.
  File  34:SciSearch(R) Cited Ref Sci 1990-2007/Feb W2
       (c) 2007 The Thomson Corp
  File  71:ELSEVIER BIOBASE 1994-2007/Feb W3
       (c) 2007 Elsevier B.V.
  File  73:EMBASE 1974-2007/Feb 19
       (c) 2007 Elsevier B.V.
  File 357:Derwent Biotech Res. _1982-2007/Feb W2
       (c) 2007 The Thomson Corp.

     Set  Items  Description
     ---  -----  -----------
Executing TE379272373
HILIGHT set on as '%'
Processing
         555  IL-11
      768949  INTERLEUKIN
     2824734  11
        6302  INTERLEUKIN(W)11
     1691141  BONE
     3239328  BINDING
     1585412  PEPTIDE?
      650788  SOLUBLE
     3872763  RECEPTOR?
  S1     121  (IL-11 OR (INTERLEUKIN (W) 11)) AND BONE AND ((BINDING
              AND PEPTIDE?) OR (SOLUBLE AND RECEPTOR?))
  S2      90  RD  (unique items)
? t s2/7/1-90;bye

 2/7/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

15117423  PMID: 15476588
 Secreted frizzled-related protein-1 inhibits RANKL-dependent osteoclast
formation.
 Hausler Karl D; Horwood Nicole J; Chuman Yoshiro; Fisher Jane L; Ellis
Jennifer; Martin T John; Rubin Jeffrey S; Gillespie Matthew T
 Bone, Joint, and Cancer Unit, St Vincent's Institute of Medical Research,
Fitzroy, Victoria, Australia.
 Journal of bone and mineral research - the official journal of the
American Society for Bone and Mineral Research (United States)  Nov 2004,
 19 (11) p1873-81, ISSN 0884-0431--Print  Journal Code: 8610640
 Publishing Model Print-Electronic
 Document type: Journal Article
 Languages: ENGLISH
 Main Citation Owner: NLM
 Record type: MEDLINE; Completed
 We determined that sFRP-1 mRNA was differentially expressed by
osteoblast/stromal cell lines and that sFRP-1 neutralizing antibodies and
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siRNA complementary to sFRP-1 coding sequence enhanced, while recombinant sFRP-1 inhibited, osteoclast formation. In studying the mechanism of action for sFRP-1, we found that sFRP-1 could bind recombinant RANKL. These results suggest potential cross-talk between Wnt and RANKL pathways. INTRODUCTION: Osteoclast formation in normal %bone% remodeling requires the presence of osteoblast lineage cells that express RANKL and macrophage-colony-stimulating factor (M-CSF), which interact with their cognate receptors on the osteoclast precursor. We identified secreted Frizzled-related protein-1 (sFRP-1), which is known to bind to Wnt and inhibit the Wnt signaling pathway, as an osteoblast-derived factor that impinges on osteoclast formation and activity. MATERIALS AND METHODS: Differential display of mRNA from osteoblast lineage cell lines established sFRP-1 to be highly expressed in an osteoclast supporting cell line. sFRP-1 expression in %bone% was determined by in situ hybridization, and the effects of sFRP-1 on osteoclast formation were determined using a neutralizing antibody, siRNA, for sFRP-1 and recombinant protein. RESULTS: In situ hybridization revealed sFRP-1 mRNA expression in osteoblasts and chondrocytes in murine %bone%. sFRP-1 mRNA expression could be elevated in calvarial primary osteoblasts in response to prostaglandin E2 (PGE2) or interleukin (IL)-11, whereas many other osteotropic agents (e.g., IL-1, IL-6, calcitrol, parathyroid hormone) were without any effect. In vitro assays of osteoclast formation established sFRP-1 to be an inhibitor of osteoclast formation. Neutralizing antibodies against sFRP-1 enhanced TRACP+ mononuclear and multinuclear osteoclast formation (3- and 2-fold, respectively) in co-cultures of murine osteoblasts with spleen cells, whereas siRNA complementary to sFRP-1 coding sequence significantly enhanced osteoclast formation in co-cultures of KUSA O (osteoblast/stromal cell line) and %bone% marrow cells, cultured in the presence of PGE2 and 1,25(OH)2 vitamin D3. Recombinant sFRP-1 dose-dependently inhibited osteoclast formation in osteoblast/spleen co-cultures, RANKL + M-CSF-treated splenic cultures, and RANKL-treated RAW264.7 cell cultures, indicating a direct action of sFRP-1 on hematopoietic cells. Consistent with this, sFRP-1 was found to bind to RANKL in ELISAs. CONCLUSION: sFRP-1 is expressed by osteoblasts and inhibits osteoclast formation. While sFRP-1 activity might involve the blocking of endogenous Wnt signaling, our results suggest that, alternatively, it could be because of direct %binding% to RANKL. This study describes a new mechanism whereby osteoblasts regulate osteoclastogenesis through the expression and release of sFRP-1.

Record Date Created: 20041012
Record Date Completed: 20050324
Date of Electronic Publication: 20040816

2/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

14382501 PMID: 12842083

A multigenic program mediating breast cancer metastasis to %bone%.

Kang Yibin; Siegel Peter M; Shu Weiping; Drobnjak Maria; Kakonen Sanna M; Cordon-Cardo Carlos; Guise Theresa A; Massague Joan

Cell Biology Program and Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Cancer cell (United States) Jun 2003, 3 (6) p537-49, ISSN 1535-6108 --Print Journal Code: 101130617

Contract/Grant No.: P01-CA94060; CA; NCI; R01-CA69158; CA; NCI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

We investigated the molecular basis for osteolytic %bone% metastasis by selecting human breast cancer cell line subpopulations with elevated metastatic activity and functionally validating genes that are overexpressed in these cells. These genes act cooperatively to cause osteolytic metastasis, and most of them encode secreted and cell surface proteins. Two of these genes, %interleukin%-%11% and CTGF, encode osteolytic and angiogenic factors whose expression is further increased by the prometastatic cytokine TGF beta. Overexpression of this %bone% metastasis gene set is superimposed on a poor-prognosis gene expression signature already present in the parental breast cancer population, suggesting that metastasis requires a set of functions beyond those underlying the emergence of the primary tumor.

Record Date Created: 20030704
Record Date Completed: 20040226

2/7/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

13254711 PMID: 11401330

Effect of %bone% morphogenetic protein-6 on haemopoietic stem cells and cytokine production in normal human %bone% marrow stroma.

Ahmed N; Sammons J; Carson R J; Khokher M A; Hassan H T

Division of Biomedical Sciences, School of Health Sciences, University of Wolverhampton, U.K.

Cell biology international (England) 2001, 25 (5) p429-35, ISSN 1065-6995--Print Journal Code: 9307129

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Normal human %bone% marrow stroma cells include stem cells for both haemopoietic and osteochondrogenic lineages and express both %bone% morphogenetic protein (BMP) type I and type II %receptors%. As a member of the TGF-beta super-family, BMP-6 binds to both BMP type I and type II %receptors% and is involved in the developmental processes of renal and hepatic systems as well as of human foetal intestine. Also, BMP-6 induces osteoblastic differentiation of pluripotent mesenchymal cells and is an autocrine stimulator of chondrocyte differentiation. The present study was carried out to investigate the effect of BMP-6 on human cobblestone-area-forming cells (CAFC), that represent the functional primitive repopulating haemopoietic stem cell in long-term %bone% marrow culture. Also, the effect of BMP-6 on marrow stroma production of interleukin-6, -11 and their common %receptor% gp130 that is expressed in haemopoietic stem cells and is indispensable for their proliferation and tri-lineage differentiation was examined. Moreover, the effect of BMP-6 on marrow stroma release of %soluble% adhesion molecule VCAM-1 mediating the primitive haemopoietic stem cell adhesion to marrow stroma was examined. The number of CAFC was significantly reduced after BMP-6 treatment from 88+/-10 per 10(5)cells in control cultures in a dose dependent manner to only 48+/-3 per 10(5)cells in 50 ng/ml BMP-6-treated cultures, $P< 0.01$. Quantitative ELISA measurement revealed 50 ng/ml BMP-6 was able to significantly reduce IL-6 and IL-11 production from marrow stroma, $P< 0.01$. Also, BMP-6 significantly increased %soluble% gp130 release by 7.4-fold in 50 ng/ml BMP-6-treated marrow stroma cultures. The profound rapid increase in this natural antagonist of human IL-6 cytokine family may reduce the gp130 signaling. Also, the %soluble% VCAM-1 released increased by two-fold in 50 ng/ml BMP-6-treated marrow stroma cultures. The marked increase in the %soluble% form may exert an antagonist effect on the function of VCAM-1 (ligand for VLA4). Recently, blocking the VLA4/VCAM-1 adhesion pathway was shown to mobilise haemopoietic CD34 positive cells in normal individuals. Also, we previously observed a significantly lower expression of VLA4 (CD49d) on G-CSF-mobilised blood CD34 positive cells than on %bone% marrow CD34 positive cells before mobilisation in the same normal donors. Since BMP are currently being used in clinical trials for %bone% repair and fracture healing, the present results suggest a possible role for BMP-6 in mobilising CD34 positive cells for transplantation. Further in vitro tests are required to evaluate this potential mobilising role of BMP-6 in human long-term %bone% marrow culture. Copyright 2001 Academic Press.

Record Date Created: 20010612
Record Date Completed: 20010802

2/7/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

12738840 PMID: 10840075
Mechanisms mediating the inhibitory effect of all-trans retinoic acid on primitive hematopoietic stem cells in human long-term %bone% marrow culture.
Sammons J; Ahmed N; Khokher M A; Hassan H T
School of Health Sciences, University of Wolverhampton, England, United Kingdom.
Stem cells (Dayton, Ohio) (UNITED STATES) 2000, 18 (3) p214-9, ISSN 1066-5099--Print Journal Code: 9304532
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
All-trans retinoic acid (RA) has generally been found to stimulate late committed (colony-forming unit- granulocyte, macrophage [CFU-GM]) and inhibit early (CFU-Blast) normal human myeloid progenitor cells. The present study provides the first evidence that the pharmacological concentration of 1 microM RA, exerts an inhibitory effect on the proliferation of functional human primitive hemopoietic stem cells (cobblestone area-forming cell [CFAC]) in long-term %bone% marrow cultures. Treatment of four-week confluent %bone% marrow culture with 1 microM RA for five days significantly reduced week 4 CAFC from 88 +/- 10 in control cultures to only 52 +/- 12 per 10(5) cells, $p < 0.01$. Quantitative enzyme-linked immunosorbent assay measurement of interleukin 6 (IL-6) and IL-11 produced from the four-week %bone% marrow stroma culture revealed only a slight and moderate increase of IL-6 and IL-11 production after treatment with RA. On the other hand, treatment with RA profoundly increased the %soluble% %receptor% gp130 released from the four-week %bone% marrow stroma by 7.5-fold from only 145 +/- 2.1 pg per ml in control cultures to 1,069.9 +/- 3.8 pg per ml in RA-treated cultures. A similar marked increase in the %soluble% adhesion molecules ICAM-1, and to a lesser extent VCAM-1, released from the four-week %bone% marrow stroma was observed after RA treatment. IL-6 has been implicated in the inhibitory effect of RA in several human hemopoietic and nonhemopoietic cells. The common transducing signal chain gp130, for all %receptors% of the IL-6 cytokine family, is expressed in most primitive human hemopoietic CD34(+) cells and its signaling was shown to synergize with other hemopoietic cytokines to expand primitive human hemopoietic stem cells. Recently, %soluble% gp130 was shown to be a natural potent antagonist of the human IL-6 cytokine family by binding the ligand and thereby reducing its bioavailability. The profound and rapid 7.5-fold increase in the natural antagonist of human IL-6 cytokine family after RA treatment could abrogate the gp130 signaling required for proliferation and/or expansion of human primitive hemopoietic stem cells and lead to the observed inhibitory effect of RA on CAFC. Both adhesion molecules VCAM-1 and ICAM-1 mediate human hemopoietic stem cell adhesion to marrow stroma. The present significant increase in the %soluble% form of these adhesion molecules after RA treatment could exert a significant antagonist effect on their function and hence may impair CAFC adhesion to marrow stroma. In conclusion, the RA inhibitory effect on the proliferation of primitive human hemopoietic stem cells could be mediated through: A) an impaired hemopoietic stem cell adhesion due to the significant increase in %soluble% adhesion molecules released from the marrow stroma after RA treatment, and B) a significantly reduced gp130 signaling that is necessary for stem cell proliferation due to the natural antagonistic effect of the profoundly increased level of %soluble% gp130 released from the marrow stroma after treatment with RA.
Record Date Created: 20000714
Record Date Completed: 20000714

2/7/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12570726 PMID: 10521086
Circulating levels of thrombopoietic and inflammatory cytokines in patients with clonal and reactive thrombocytosis.
Hsu H C; Tsai W H; Jiang M L; Ho C H; Hsu M L; Ho C K; Wang S Y
Department of Medicine, Veterans General Hospital-Taipei, Taiwan, Republic of China.
Journal of laboratory and clinical medicine (UNITED STATES) Oct 1999, 134 (4) p392-7, ISSN 0022-2143--Print Journal Code: 0375375
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The regulation of megakaryocytopoiesis and thrombopoiesis appears to be under the control of an array of hematopoietic growth factors. To determine the relationship between endogenous cytokine levels and circulating platelet counts, we measured the serum levels of both thrombopoietic and inflammatory cytokines in the peripheral blood and %bone% marrow samples from 70 patients with clonal thrombocytosis (CT) caused by myeloproliferative disorders, 28 patients with reactive thrombocytosis (RT), and 35 normal control subjects. The levels of thrombopoietin (TPO), interleukin-6 (IL-6), %soluble% IL-6 (sIL-6) %receptor%, IL-11, stem cell factor (SCF), IL-3, and IL-8 were determined by enzyme-linked immunosorbent assay (ELISA). Platelet counts were significantly higher in both CT and patients with RT (699+/-399x10(9)/L, P<.001; 642+/-200 x 10(9)/L, P<.001; respectively) as compared with the normal control subjects (240+/-47x10(9)/L). The concentrations of cytokines in the %bone% marrow correlated well with those in the peripheral blood. The endogenous levels of TPO, IL-6, and sIL-6 %receptor% were significantly higher in both CT and patients with RT than those in normal control subjects. The median level of IL-6 was significantly higher in patients with RT than in patients with CT (40 pg/mL vs. 5 pg/mL; P<.001); however, there was no detectable difference in TPO and sIL-6 %receptor% levels between the two groups. Significantly higher levels of SCF and IL-8 were also found in patients with CT as compared with those found in normal control subjects (median 2460 pg/mL vs 1995 pg/mL, P<.05; 20 ng/mL vs. 5 ng/mL, P = .001; respectively). Finally, IL-11 and IL-3 levels were undetectable in most patients with thrombocytosis. Our results reveal that the endogenous levels of TPO, IL-6, sIL-6 %receptor% , IL-8, and SCF are elevated in patients with CT or RT. These cytokines appear to be active mediators involved in the regulation of thrombopoiesis during clonal and reactive thrombocytosis.
Record Date Created: 19991025
Record Date Completed: 19991025

2/7/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12549404 PMID: 10496948
The hemoregulatory %peptide% pEEDCK may inhibit stem cell proliferation via hydropathic %binding% to antisense sequence motifs in %interleukin%-%11% and other growth factors.
Paukovits J B; Rutter R; Ganglberger E; Karlic H I; Marian B; Paukovits W R
Institute of Tumorbiology-Cancer Research, University of Vienna, Vienna, Austria. walter.paukovits@univie.ac.at
Molecular pharmacology (UNITED STATES) Oct 1999, 56 (4) p665-74, ISSN 0026-895X--Print Journal Code: 0035623
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
In undisturbed %bone% marrow, most hemopoietic stem cells are nonproliferating despite the presence of multiple growth factors. Endogenous inhibitory factors are responsible for maintenance of this quiescence. Previously we sequenced and synthesized the inhibitory pentapeptide pGlu-Glu-Asp-Cys-Lys (pEEDCK), which originally derives from granulocytes, and investigated the role of this %peptide% in stem cell quiescence. To provide some mechanistic insight, in the present work we studied the structural relationship of this %peptide% to specific growth-factor-derived sequence motifs. In the murine system in vivo as well as in long-term %bone% marrow, antiserum to pEEDCK produced a significant

stimulation of formation of colony-forming units-granulocyte/macrophage. %Binding% of %peptides% to proteins often takes place at hydropathically complementary sites. Therefore, we searched for %peptides% corresponding to the complementary sequence to pEEDCK. We identified antisense sequences in the genes of various cytokines and cytokine receptors including %interleukin%-%11%. The corresponding %peptide% Val-Leu-Leu-Thre-Arg (VLLTR) and several other %peptides% hydropathically complementary to pEEDCK were synthesized. We found that pEEDCK binds specifically to these %peptides% as well as to complete %interleukin%-%11% . Dissociation constants were in the 10 microM range. The %peptide% hydropathically corresponding to pEEDCK (VLLTR) was found to stimulate colony-forming units-granulocyte/macrophage formation. Our data suggest that pEEDCK could exert a coordinating function in the hemopoietic cytokine network by %binding% to multiple regulatory proteins and modulating their activity.
Record Date Created: 19991008
Record Date Completed: 19991008

2/7/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12121844 PMID: 10564261
Chimeric cytokine %receptor% can transduce expansion signals in interleukin 6 %receptor% alpha (IL-6Ralpha)-, IL-11Ralpha-, and gp130-low to -negative primitive hematopoietic progenitors.
Takagi M; Nakamura T; Sawada T; Kaneko A; Nozaki-Ukai M; Nakahata T; Yokota T; Heike T
Department of Stem Cell Regulation, Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan.
Molecular biology of the cell (UNITED STATES) Nov 1999, 10 (11) p3633-42, ISSN 1059-1524--Print Journal Code: 9201390
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We generated transgenic mice expressing chimeric %receptors%, which comprise extracellular domains of the human granulocyte-macrophage colony-stimulating factor (hGM-CSF) %receptor% and transmembrane and cytoplasmic domains of the mouse leukemia inhibitory factor %receptor%. In suspension cultures of lineage-negative (Lin(-)), 5-fluorouracil-resistant %bone% marrow cells of the transgenic mice, a combination of hGM-CSF and stem cell factor (SCF) induced exponential expansions of mixed colony-forming unit. The combination of hGM-CSF and SCF was effective on enriched, Lin(-)Sca-1(+)c-kit(+) progenitors and increased either mixed colony-forming unit or cobblestone area-forming cells. In case of stimulation with hGM-CSF and SCF, interleukin-6 (IL-6) and SCF, or IL-11 and SCF, the most efficient expansion was achieved with hGM-CSF and SCF. When Lin(-)Sca-1(+)c-kit(+)CD34(-) further enriched progenitors were clone sorted and individually incubated in the presence of SCF, hGM-CSF stimulated a larger number of cells than did IL-6, IL-6 and %soluble% IL-6 %receptor% (IL-6R), or IL-11. These data suggest the presence of IL-6Ralpha-, IL-11Ralpha-, and gp130-low to -negative primitive hematopoietic progenitors. Such primitive progenitors are equipped with signal transduction molecules and can expand when these chimeric %receptors% are genetically introduced into the cells and stimulated with hGM-CSF in the presence of SCF.
Record Date Created: 19991209
Record Date Completed: 19991209

2/7/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11998025 PMID: 9824538
Interleukin-6-type cytokines stimulate mesenchymal progenitor differentiation toward the osteoblastic lineage.
Taguchi Y; Yamamoto M; Yamate T; Lin S C; Mocharla H; DeTogni P; Nakayama N; Boyce B F; Abe E; Manolagas S C
Department of Internal Medicine, Center for Osteoporosis and Metabolic Bone Diseases, and the McClellan VA GRECC, University of Arkansas for Medical Sciences, Little Rock 72205, USA.
Proceedings of the Association of American Physicians (UNITED STATES) Nov-Dec 1998, 110 (6) p559-74, ISSN 1081-650X--Print Journal Code: 9514310
Contract/Grant No.: AR 41313; AR; NIAMS; PO1 AG139181; AG; NIA
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Cytokines that transduce their signals either through glycoprotein 130 (gp130) homodimers or gp 130/leukemia inhibitory factor (LIF) %receptor% beta heterodimers are potent inducers of osteoclast development in vitro as well as in vivo; and interleukin (IL)-6 has been recognized as an important pathogenic factor in diseases characterized by increased %bone% remodeling, such as the osteoporosis of sex steroid deficiency. Based on evidence that the same cytokines can also promote committed osteoblast differentiation and stimulate %bone% formation in vitro and in vivo and that mesenchymal cell differentiation toward the osteoblast lineage may be a prerequisite for osteoclastogenesis, we have investigated whether gp130 activation can affect the differentiation of uncommitted mesenchymal progenitors. Using as our model murine embryonic fibroblasts (EF), we found that IL-6 or IL-11 in combination with their %soluble% %receptors% (sIL-6R or sIL-11R) increased dose-dependently the number of alkaline phosphatase (AP)-positive cells in 3-6-day-long cultures. Moreover, EF cells maintained with IL-6/sIL-6R in the presence of ascorbic acid and beta-glycerophosphate expressed osteocalcin messenger RNA (mRNA) by 2 weeks and formed a matrix containing mineralized collagen fibers by 3 weeks. This prodifferentiation effect was specific for the osteoblastic lineage, as we found no evidence for increased differentiation of chondrocytes, adipocytes, or muscle cells. Unlike IL-6/sIL-6R, LIF, oncostatin M (OSM), and ciliary neurotrophic factor (CNTF) did not promote osteoblastic differentiation of EF cells. This pattern of specificity was accounted for by the finding that EF cells express gp130, but not the ligand-binding subunit of the IL-6 %receptor% (gp80) nor the LIF %receptor% beta. These observations add credence to the contention that increased production of gp130-utilizing cytokines and their %receptors% in pathological conditions like sex steroid deficiency is indeed responsible for not only the increased osteoclastogenesis, but also the increased osteoblastogenesis, and thereby for the increased rate of %bone% remodeling.
Record Date Created: 19990125
Record Date Completed: 19990125

2/7/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11904452 PMID: 9732294
Mode of action of interleukin-6 on mature osteoclasts. Novel interactions with extracellular Ca2+ sensing in the regulation of osteoclastic %bone% resorption.
Adebanjo O A; Moonga B S; Yamate T; Sun L; Minkin C; Abe E; Zaidi M
Center for Osteoporosis and Skeletal Aging, Veterans Affairs Medical Center, and Department of Medicine, Medical College of Pennsylvania-Hahnemann School of Medicine, Philadelphia, Pennsylvania 19104, USA.
Journal of cell biology (UNITED STATES) Sep 7 1998, 142 (5) p1347-56 , ISSN 0021-9525--Print Journal Code: 0375356
Contract/Grant No.: RO1 AG14917-02; AG; NIA
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We describe a physiologically significant mechanism through which interleukin-6 (IL-6) and a rising ambient Ca2+ interact to regulate

osteoclastic %bone% resorption. VOXEL-based confocal microscopy of nonpermeabilized osteoclasts incubated with anti- IL-6 %receptor% antibodies revealed intense, strictly peripheral plasma membrane fluorescence. IL-6 %receptor% expression in single osteoclasts was confirmed by in situ reverse transcriptase PCR histochemistry. IL-6 (5 ng/l to 10 microg/l), but not IL-11 (10 and 100 microg/l), reversed the inhibition of osteoclastic %bone% resorption induced by high extracellular Ca2+ (15 mM). The IL-6 effect was abrogated by excess %soluble% IL-6 %receptor% (500 microg/l). Additionally, IL-6 (5 pg/l to 10 microg/l) inhibited cytosolic Ca2+ signals triggered by high Ca2+ or Ni2+. In separate experiments, osteoclasts incubated in 10 mM Ca2+ or on %bone% released more IL-6 than those in 1.25 mM Ca2+. Furthermore, IL-6 mRNA histostaining was more intense in osteoclasts in 10 or 20 mM Ca2+ than cells in 1.25 mM Ca2+. Similarly, IL-6 %receptor% mRNA histostaining was increased in osteoclasts incubated in 5 or 10 mM Ca2+. Thus, while high Ca2+ enhances IL-6 secretion, the released IL-6 attenuates Ca2+ sensing and reverses inhibition of resorption by Ca2+. Such an autocrine-paracrine loop may sustain osteoclastic activity in the face of an inhibitory Ca2+ level generated locally during resorption.
Record Date Created: 19981021
Record Date Completed: 19981021

2/7/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11803321 PMID: 9626137
In vitro secretion of cytokines by human %bone% marrow: effects of age and estrogen status.
Cheleuitte D; Mizuno S; Glowacki J
Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
Journal of clinical endocrinology and metabolism (UNITED STATES) Jun 1998, 83 (6) p2043-51, ISSN 0021-972X--Print Journal Code: 0375362
Contract/Grant No.: AG-12271; AG; NIA; AG-13519; AG; NIA
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
It has been proposed that cytokines mediate the acceleration of %bone% loss following menopause. Because of the intimate relationship between %bone% marrow stromal cells and %bone% tissue, it is possible that marrow cells and their products contribute to the %bone% microenvironment and influence the regulation of %bone% cell differentiation and activity. We examined the production of cytokines by %bone% marrow stromal cells from a total of 37 women and 15 men undergoing total hip replacement for noninflammatory joint disease. Low-density mononuclear cells were isolated from %bone% marrow and were cultured in phenol red-free alpha MEM medium supplemented with 10% FBS and antibiotics. Constitutive secretion of interleukin-6 (IL-6) was positively correlated with age in a series of 8 women and 5 men measured by bioassay ($r = 0.98$; $P < 0.01$) and in a series of 18 women and 10 men measured by immunoassay ($r = 0.56$; $P < 0.01$). The pattern of cytokine production by %bone% marrow stromal cells was examined in detail in 23 postmenopausal women, aged 49-88 yr. Basal secretion of immunoreactive IL-6 and IL-11, but not granulocyte-macrophage colony-stimulating factor, increased with time in culture. Exogenous IL-1 beta stimulated secretion of IL-6 and IL-11 in a saturable, dose-dependent manner. Secretion of %soluble% IL-6 %receptor% was not correlated with secretion of IL-6, either constitutively or in the presence of IL-1 beta. In 4 of 14 samples, IL-1 beta also stimulated secretion of granulocyte-macrophage colony-stimulating factor. IL-1 beta was undetectable in 7 of 9 cultures during the 2-week culture period. IL-6 did not stimulate secretion of IL-1 beta in the 7 cultures tested. Cells were dependent upon serum for viability and growth and were not sustained by a serum substitute (1% insulin-transferrin-selenium-BSA). Cells grown in medium with 10% FBS and supplemented with 1% insulin-transferrin-selenium-BSA secreted 10-fold more IL-6 than cells grown in serum alone. Marrow from 7 women receiving estrogen replacement therapy showed lower constitutive secretion of IL-6 (75%; $P < 0.006$) and IL-11 (43%; $P < 0.05$) than marrow from age-matched controls and had blunted stimulation of IL-6 and IL-11 secretion by exogenous IL-1 beta. These data indicate distinct patterns of cytokine production by human marrow stromal cultures dependent upon age and estrogen status.
Record Date Created: 19980702
Record Date Completed: 19980702

2/7/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11113544 PMID: 8940087
Functional expression of %soluble% human %interleukin%-%11% (IL-11) %receptor% alpha and stoichiometry of in vitro IL-11 %receptor% complexes with gp130.
Neddermann P; Graziani R; Ciliberto G; Paonessa G
Istituto di Ricerche di Biologia Molecolare "P. Angeletti" (IRBM), Department of Genetics, 00040 Pomezia (Roma), Italy. Neddermann@IRBM.it
Journal of biological chemistry (UNITED STATES) Nov 29 1996, 271 (48) p30986-91, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The interleukin-6 (IL-6) family of cytokines activates signaling through the formation of either gp130 homodimers, as for IL-6, or gp130-leukemia inhibitory factor %receptor% (LIFR) heterodimers as for ciliary neurotrophic factor (CNTF), leukemia inhibitory factor, oncostatinM, and cardiotrophin-1. Recent in vitro studies with IL-6 and CNTF have demonstrated that higher order hexameric %receptor% complexes are assembled in which signaling chain dimerization is accompanied by the dimerization of both the cytokine molecule and its specific %receptor% alpha subunits (IL-6Ralpha or CNTFRalpha, respectively). IL-11 is a member of the IL-6 family and known to require gp130 but not LIFR for signaling. In this study we investigate the functional and biochemical composition of the IL-11 %receptor% complex. The human IL-11 %receptor% alpha-chain was cloned from a human %bone% marrow cDNA library. IL-11Ralpha was shown to confer IL-11 responsiveness to human hepatoma cells either by cDNA transfection or by adding a %soluble% form of the %receptor% (sIL11Ralpha) expressed in the baculovirus system to the culture medium. In vitro immunoprecipitation experiments showed that sIL11Ralpha specifically binds IL-11 and that binding is enhanced by gp130. Similarly to IL-6 and CNTF, gp130 is able to induce dimerization of the IL-11.IL-11Ralpha subcomplex, the result of which is the formation of a pentameric %receptor% complex. However, in contrast to the other two cytokines, IL-11 was unable to induce either gp130 homodimerization or gp130/LIFR heterodimerization. These results strongly suggest that an as yet unidentified %receptor% beta-chain is involved in IL-11 signaling.
Record Date Created: 19970107
Record Date Completed: 19970107

2/7/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10895555 PMID: 8676079
The role of gp130-mediated signals in osteoclast development: regulation of %interleukin% %11% production by osteoblasts and distribution of its %receptor% in %bone% marrow cultures.
Romas E; Udagawa N; Zhou H; Tamura T; Saito M; Taga T; Hilton D J; Suda T ; Ng K W; Martin T J
St. Vincent's Institute of Medical Research, University of Melbourne, Victoria, Australia.
Journal of experimental medicine (UNITED STATES) Jun 1 1996, 183 (6) p2581-91, ISSN 0022-1007--Print Journal Code: 2985109R
Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Interleukin (IL)-11 is a multifunctional cytokine whose role in osteoclast development has not been fully elucidated. We examined IL-11 production by primary osteoblasts and the effects of rat monoclonal anti-mouse glycoprotein 130 (gp130) antibody on osteoclast formation, using a coculture of mouse osteoblasts and %bone% marrow cells. IL-1, TNF alpha, PGE2, parathyroid hormone (PTH) and 1 alpha,25-dihydroxyvitamin D3 (1 alpha,25(OH)2D3) similarly induced production of IL-11 by osteoblasts, but IL-6, IL-4, and TGF beta did not. Primary osteoblasts constitutively expressed mRNAs for both IL-11 %receptor% (IL-11R alpha) and gp130. Osteotropic factors did not modulate IL-11R alpha mRNA at 24 h, but steady-state gp130 mRNA expression in osteoblasts was upregulated by 1 alpha,25(OH)2D3, PTH, or IL-1. In cocultures, the formation of multinucleated osteoclast-like cells (OCLs) in response to IL-11, or IL-6 together with its %soluble% IL-6 %receptor% was dose-dependently inhibited by rat monoclonal anti-mouse gp130 antibody. Furthermore, adding anti-gp130 antibody abolished OCL formation induced by IL-1, and partially inhibited OCL formation induced by PGE2, PTH, or 1 alpha,25(OH)2D3. During osteoclast formation in marrow cultures, a sequential relationship existed between the expression of calcitonin %receptor% mRNA and IL-11R alpha mRNA. Osteoblasts as well as OCLs expressed transcripts for IL-11R alpha, as indicated by RT-PCR analysis and in situ hybridization. These results suggest a central role of gp130-coupled cytokines, especially IL-11, in osteoclast development. Since osteoblasts and mature osteoclasts expressed IL-11R alpha mRNA, both %bone%-forming and %bone%-resorbing cells are potential targets of IL-11.

Record Date Created: 19960815
Record Date Completed: 19960815

2/7/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10603061 PMID: 8579904
Modulation of osteoclast differentiation by local factors.
Suda T; Udagawa N; Nakamura I; Miyaura C; Takahashi N
Department of Biochemistry, School of Dentistry, Showa University, Tokyo, Japan.
Bone (UNITED STATES) Aug 1995, 17 (2 Suppl) p87S-91S, ISSN 8756-3282--Print Journal Code: 8504048
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

%Bone% -resorbing osteoclasts are of hemopoietic cell origin, probably of the CFU-M-derived monocyte-macrophage family. %Bone% marrow-derived osteoblastic stromal cells play an important role in modulating the differentiation of osteoclast progenitors in two different ways: one is the production of %soluble% factors, and the other is cell-to-cell recognition between osteoclast progenitors and osteoblastic stromal cells. M-CSF is probably the most important %soluble% factor, which appears to be necessary for not only proliferation of osteoclast progenitors, but also differentiation into mature osteoclasts and their survival. A number of local factors as well as systemic hormones induce osteoclast differentiation. They are classified into three categories in terms of the signal transduction: vitamin D %receptor% -mediated signals [1 alpha,25(OH)2D3]; protein kinase A-mediated signals (PTH, PTHrP, PGE2, and IL-1); and gp130-mediated signals (IL-6, IL-11, oncostatin M, and leukemia inhibitory factor). All of these osteoclast-inducing factors appear to act on osteoblastic cells to commonly induce osteoclast differentiation factor (ODF), which recognizes osteoclast progenitors and prepares them to differentiate into mature osteoclasts. This line of approach will undoubtedly produce new ways to treat several metabolic %bone% diseases caused by abnormal osteoclast recruitment such as osteoporosis, osteopetrosis, Paget's disease, rheumatoid arthritis, and periodontal disease. (30 Refs.)

Record Date Created: 19960320
Record Date Completed: 19960320

2/7/14 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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18988277 BIOSIS NO.: 200600333672
Osteoporosis treatment with anti-IL-11 antibody
AUTHOR: Shaughnessy Stephen; Austin Richard Carl
AUTHOR ADDRESS: St. Catharines, ON L8V 1C3, Canada**Canada
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents FEB 14 2006 2006
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: There is disclosed a process of treating or alleviating the symptoms of pathological conditions in which %bone% density is decreased, which comprises inhibiting, in a mammalian patient suffering from such a condition, the formation in vivo of a tertiary complex of IL-11, its cell surface membrane %receptor% and the cell surface glycoprotein gp130. Examples of such substances are recombinant %soluble% IL-11 %receptor% mutants modified, as compared with native IL-11 %receptor%, at their gp130 %binding% site, and %peptides% which can interact with IL-11. The process of the invention not only inhibits %bone% resorption and hence %bone% loss, but also increases the process of %bone% formation to increase %bone% density.

2/7/15 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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18854991 BIOSIS NO.: 200600200386
IL-11 and IL-6 stimulation of osteoclast formation depends on STAT- but not ERK-mediated pathways in ostcoblasts.
AUTHOR: Quinn J M W (Reprint); Nakamura A; Jenkins B J; Sims N A; Ernst M; Martin T J; Gillespie M T
AUTHOR ADDRESS: St Vincents Inst Med Res, Bone Joint and Canc Grp, Fitzroy, Vic 3065, Australia**Australia
JOURNAL: Journal of Bone and Mineral Research 20 (9, Suppl. 1): pS375 SEP 2005 2005
CONFERENCE/MEETING: 27th Annual Meeting of the American-Society-for-Bone-and-Mineral-Research Nashville, TN, USA September 23 -27, 2005; 20050923
SPONSOR: Amer Soc Bone & Mineral Res
ISSN: 0884-0431
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/16 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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18660005 BIOSIS NO.: 200600005400
Increased expression of interleukin-6 by vasoactive intestinal %peptide% is associated with regulation of CREB, AP-1 and C/EBP, but not NF-kappa B, in mouse calvarial osteoblasts
AUTHOR: Persson Emina (Reprint); Voznesensky Olga S; Huang Yu-Feng; Lerner Ulf H
AUTHOR ADDRESS: Umea Univ, Dept Oral Cell Biol, SE-90187 Umea, Sweden** Sweden
AUTHOR E-MAIL ADDRESS: emma.persson@odont.umu.se
JOURNAL: Bone (New York) 37 (4): p513-529 OCT 2005 2005

ISSN: 8756-3282
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interleukin-6 (IL-6), and the related cytokines IL- 11, leukemia inhibitory factor (LIF) and oncostatin M (OSM), are potent stimulators of osteoclastic %bone% resorption. In the present study, we have addressed the possibility that the neuropeptide vasoactive intestinal %peptide% (VIP) may regulate the production of and/or sensitivity to the IL-6 family of cytokines in mouse calvarial osteoblasts. VIP stimulated IL-6 mRNA expression and protein release in a time- and concentration-dependent manner, whereas mRNA expression of the IL-6 receptor, as well as mRNA expressions of IL-11, LIF, OSM and their cognate receptors, were unaffected by VIP. In cells transfected with the IL-6 promoter coupled to luciferase, VIP increased transcriptional activity. The effects of VIP were shared by the related neuropeptide PACAP-38, belonging to the same superfamily of neuropeptides, whereas secretin did not have any effect, indicating that the effects were mediated by VPAC2 receptors. The effects of VIP were potentiated by the cyclic AMP phosphodiesterase inhibitor rolipram and mimicked by forskolin, indicating the involvement of the cyclic AMP/protein kinase A pathway. This was further demonstrated by the facts that the stimulatory effect of VIP on luciferase activity could be reversed by the PKA inhibitors H-89 and KT5720 and was mimicked by cyclic AMP analogues selective for PKA, but not by those selective for Epac. In addition, VIP enhanced the phosphorylation of CREB, as assessed by both immumocytochemical analysis and Western blot. The DNA %binding% activity of nuclear extracts to C/EBP was increased by VIP, whereas %binding% to AP-1 was decreased. In contrast, DNA %binding% to NF-kappa B, as well as nuclear translocation of NF-kappa B and C/EBP, were unaffected by VIP. The mRNA expressions of C/EBP beta, C/EBP gamma, C/EBP gamma, c-Jun, JunB, c-Fos, Fra-l and I kappa B alpha and protein level of I kappa B alpha were all unaffected by VIP. These observations, together, demonstrate that VIP stimulates IL-6 production in osteoblasts by a mechanism likely to be mediated by VPAC2 receptors and dependent on cyclic AMP/protein kinase A/CREB activation and also involving the transcription factors C/EBP and AP-1. (c) 2005 Elsevier Inc. All rights reserved.

2/7/17 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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18649789 BIOSIS NO.: 200510344289
Osteoporosis treatment
AUTHOR: Shaughnessy Stephen; Austin Richard Carl
AUTHOR ADDRESS: St. Catharines, Canada**Canada
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents JAN 25 2005 2005
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: There is disclosed a process of treating or alleviating the symptoms of pathological conditions in which %bone% density is decreased, which comprises inhibiting, in a mammalian patient suffering from such a condition, the formation in vivo of a tertiary complex of IL-11, its cell surface membrane %receptor% and the cell surface glycoprotein gp130. Examples of such substances are recombinant %soluble% IL-11 %receptor% mutants modified, as compared with native IL-11 %receptor%, at their gp130 %binding% site, and %peptides% which can interact with IL-11. The process of the invention not only inhibits %bone% resorption and hence %bone% loss, but also increases the process of %bone% formation to increase %bone% density.

2/7/18 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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18307628 BIOSIS NO.: 200510002128
RANK, RANKL and osteoprotegerin in arthritic %bone% loss
AUTHOR: Bezerra M C; Carvalho J F; Prokopowitsch A S; Pereira R M R (Reprint)
AUTHOR ADDRESS: USP, FM, Dept Reumatol, Av Dr Arnaldo,455,Sala 3107, BR-01246903 Sao Paulo, Brazil**Brazil
AUTHOR E-MAIL ADDRESS: rosamariarp@yahoo.com
JOURNAL: Brazilian Journal of Medical and Biological Research 38 (2): p 161-170 FEB 05 2005
ISSN: 0100-879X
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Rheumatoid arthritis is characterized by the presence of inflammatory synovitis and destruction of joint cartilage and %bone%. Tissue proteinases released by synovia, chondrocytes and pannus can cause cartilage destruction and cytokine-activated osteoclasts have been implicated in %bone% erosions. Rheumatoid arthritis synovial tissues produce a variety of cytokines and growth factors that induce monocyte differentiation to osteoclasts and their proliferation, activation and longer survival in tissues. More recently, a major role in %bone% erosion has been attributed to the %receptor% activator of nuclear factor kappa B ligand (RANKL) released by activated lymphocytes and osteoblasts. In fact, osteoclasts are markedly activated after RANK-L %binding% to the cognate RANK expressed on the surface of these cells. RANKL expression can be upregulated by %bone%-resorbing factors such as glucocorticoids, vitamin D3, interleukin 1 (IL-1), IL-6, IL-11, IL-17, tumor necrosis factor-alpha, prostaglandin E-2, or parathyroid hormone-related %peptide% . Supporting this idea, inhibition of RANKL by osteoprotegerin, a natural %soluble% RANKL %receptor%, prevents %bone% loss in experimental models. Tumor growth factor-beta released from %bone% during active %bone% resorption has been suggested as one feedback mechanism for upregulating osteoprotegerin and estrogen can increase its production on osteoblasts. Modulation of these systems provides the opportunity to inhibit %bone% loss and deformity in chronic arthritis.

2/7/19 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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17781783 BIOSIS NO.: 200400148444
Unveiling the molecular signature of a lung homing "hotspot" of hematopoietic stem cells with phagemid display: Implications for tissue conversions.
AUTHOR: Cerny Jan (Reprint); Demers Delia; Dooner Mark S; Menon Mary K; Pimentel Jeffrey; Colvin Gerald A; Abedi Mehrdad; Greer Deborah; Quesenberry Peter J
AUTHOR ADDRESS: Department of Medicine, University of Massachusetts, Worcester, MA, USA**USA
JOURNAL: Blood 102 (11): p840a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have previously showed that the phenotype of the hematopoietic stem cell (HSC) changes dramatically during cytokine-stimulated cell cycle transit. Culture of Lin-Sca+ cells in IL-3, IL-6, IL-11 and steel factor led to decreased marrow homing 3 hours after cell infusion from cells cultured for 24 and 48 hours as compared to input cells (Cerny et al. J Hematother Stem Cell Res 2002; 11: 913). In further studies we have

determined that 24 hour cultured Lin-Sca+ cells labeled with CFSE show approximately a ten-fold higher number of fluorescent events in the lung as compared to input cells. We termed this a lung "homing hotspot". Phage display biopanning is a powerful technique allowing for detection of predominant surface %peptides% on a cell population. We have used this approach to biopan %bone% marrow (BM) cells at 0 and 24 hours of culture. A lung specific phagemid display cDNA library (PhDL) was selected because of the apparent directed homing of BM cells to lung tissue. We thus performed in vitro panning of this PhDL with BM cells at 0 and 24 hours of culture with IL-3, IL-6, IL-11 and steel factor. We designed our experiments with different subtractive panning approaches: A - PhDL bound to 0 hr cells in 4 sequential rounds; B- PhDL initially bound to 0 hrs cells and panned 4X on 24 hrs cultured cells; C- initial supernatant PhDL that did not bind to 0 hr cells were 4X panned on 24 hrs cells 1; D- each round 0 hr supernatant PhDL cells were panned on 24 hrs cells. Titers of PhDLs suggested that A-clones saturated the system early (common %binding% phage) while slow increase due to selective %binding% of PhDL was seen in clones B, C and D. Sequencing of selected PhDLs retrieved several predominant sequences. MouseBLAST search revealed homology of the PhDL interacting with 0 hr BM cells to beta-chimerin (p21 -Rac family protein). The phagemid that showed no %binding% to 0 hour cells, but bound to 24 hour ("lung hotspot") cells showed homology to Rock1 Rho-associated coiled-coil forming kinase 1. Both these proteins are involved in cell motility and cell adhesion to endothelium and extracellular matrix. We believe that these %peptide% sequences are important for BM cells homing to lung tissue.

2/7/20 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17379949 BIOSIS NO.: 200300336692
Megakaryocytes Derived from Embryonic Stem Cells Implicate Exchange Factor CalDAG-GEFI in Integrin Signaling.
AUTHOR: Eto Koji (Reprint); Murphy Ronan (Reprint); Kerrigan Steve W (Reprint); Bertoni Alessandra (Reprint); Stuhlman Heidi (Reprint); Nakano Toru (Reprint); Leavitt Andrew D (Reprint); Shattil Sanford J (Reprint)
AUTHOR ADDRESS: Cell Biology, The Scripps Research Institute, La Jolla, CA, USA**USA
JOURNAL: Blood 100 (11): pAbstract No. 1994 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Fibrinogen %binding% to integrin alphaIIbbeta3 mediates platelet aggregation and requires agonist-induced "inside-out" signals that increase alphaIIbbeta3 affinity. Agonist regulation of alphaIIbbeta3 also takes place in megakaryocytes, the %bone% marrow cells from which platelets are derived. To facilitate mechanistic studies of inside-out signaling and other aspects of megakaryocyte and platelet biology, we describe here the generation of megakaryocytes in quantity from murine embryonic stem (ES) cells. Co-culture of R1 ES cells for 8-12 days with OP9 stromal cells in the presence of thrombopoietin, IL-6, IL-11 and serum resulted in the sequential development of small megakaryocyte progenitors, intermediate-size young megakaryocytes, and large, mature megakaryocytes that produced proplatelets. Typically, an initial culture of 1 X 104 ES cells yielded 6 X 104 viable, alphaIIbbeta3-expressing cells on day 12, of which two-thirds were intermediate and large megakaryocytes. Similar results were obtained starting with two other commonly used ES cell lines, E14 and W4/129S6. The large megakaryocytes derived from ES cells exhibited high DNA ploidy (16-128n) and expressed platelet glycoprotein Ibalpha, but they were devoid of hematopoietic stem cell, erythrocyte and leukocyte markers. ES cell-derived megakaryocytes, but not megakaryocyte progenitors, specifically bound fibrinogen via alphaIIbbeta3 in response to platelet agonists, such as a PAR4 thrombin receptor-activating %peptide%, ADP and epinephrine. Infection of cells on day five of the differentiation protocol with a recombinant retrovirus encoding the reporter gene, GFP, led subsequently to the expression of GFP in 10-50% of mature megakaryocytes, with no adverse effects on cell viability or alphaIIbbeta3 function. However, retroviral expression of CalDAG-GEFI, a Rap1 exchange factor identified by megakaryocyte gene profiling as a candidate integrin regulator, enhanced agonist-induced activation of Rap1b and fibrinogen %binding% to alphaIIbbeta3 ($P < 0.01$). These results establish that embryonic stem cells are a ready source of megakaryocytes for studies of integrin signaling, megakaryocytopoiesis and platelet development. Moreover, they demonstrate that ES cell-derived megakaryocytes provide a biologically relevant system to determine the role of candidate genes in alphaIIbbeta3 function, as exemplified by CalDAG-GEFI. Indeed, since the Rap1b exchange activity of CalDAG-GEFI is regulated by calcium and diacylglycerol, and Rap1b promotes affinity modulation of alphaIIbbeta3, CalDAG-GEFI may represent a previously unknown but critical link between platelet agonist receptors and alphaIIbbeta3.

2/7/21 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16808070 BIOSIS NO.: 200200401581
Evidence that the IL-6/IL-6 %soluble% %receptor% cytokine system plays a role in the increased skeletal sensitivity to PTH in estrogen-deficient women
AUTHOR: Masiukiewicz Urszula S (Reprint); Mitnick Maryann; Gulanski Barbara I; Insogna Karl L
AUTHOR ADDRESS: Yale University School of Medicine, 333 Cedar Street, FMP 109, P.O. Box 208020, New Haven, CT, 06520-8020, USA**USA
JOURNAL: Journal of Clinical Endocrinology and Metabolism 87 (6): p 2892-2898 June, 2002 2002
MEDIUM: print
ISSN: 0021-972X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Estrogen-deficient women show increased skeletal sensitivity to the resorbing actions of PTH. The basis for this effect is not known. To examine the influence of estrogen deficiency on PTH-induced proresorptive cytokine production in humans, the response of five young women to a 36-h infusion of (1-34)human PTH (hPTH) was studied. PTH induced significant increases in circulating levels of IL-6 (mean values, T0fwdarwT36 h; 2.2fwdarw19.2 pg/ml), IL-6 %soluble% %receptor% (IL-6sR; 29.8fwdarw67.2 ng/ml), urine N-telopeptide of type I collagen (NTX) (38.6fwdarw148 nM %bone% collagen equivalent/mM creatinine) and serum calcium (2.12fwdarw2.62 mmol/liter). To examine the impact of hormonal status on this response, PTH infusions were next undertaken in seven estrogen-deficient and seven estrogen-treated post-menopausal women. When compared with estrogen-treated women, and correcting for differences in baseline values, estrogen-deficient women demonstrated an exaggerated increase in circulating levels of IL-6 (5.0fwdarw31.7 vs. 3.2fwdarw14.4 pg/ml; $P = 0.0001$) and IL-6sR (49.2fwdarw102.1 vs. 37.7fwdarw66.7; $P = 0.0001$). This was accompanied by greater increases in NTX excretion in the estrogen-deficient women (61.2fwdarw201.6 vs. 44.8fwdarw114.8, E- vs. E+, $P = 0.0001$). Estrogen deficiency was not associated with augmented PTH-induced increases in colony-stimulating factor-1, IL-1beta, IL-11, or TNF-alpha. In a multiple regression model controlling for group, age, years since menopause both IL-6 and IL-6sR were strong predictors of NTX. These data, along with previous animal studies, support the conclusion that the IL-6/IL-6SR cytokine system plays a role in the increased skeletal sensitivity to PTH seen in estrogen-deficient women.

2/7/22 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16496650 BIOSIS NO.: 200200090161
Human PTH-(7-84) inhibits %bone% resorption in vitro via actions independent of the type 1 PTH/PTHrP receptor
AUTHOR: Divieti P (Reprint); John M R; Juppner H; Bringhurst F R
AUTHOR ADDRESS: Endocrine Unit, Massachusetts General Hospital, Harvard Medical School, Wellman 5, Boston, MA, 02114, USA**USA
JOURNAL: Endocrinology 143 (1): p171-176 January, 2002 2002
MEDIUM: print
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The linear sequence of intact mammalian PTH consists of 84 amino acids, of which only the most amino(N)-terminal portion, i.e. PTH-(1-34), is required for the classical actions of the hormone on mineral ion homeostasis mediated by the type 1 PTH/PTHrP receptor (PTH1R). Like the N-terminus, the carboxyl (C)-terminal sequence of PTH is highly conserved among species, and various circulating PTH C-fragments are generated by peripheral metabolism of intact PTH or are directly secreted, in a calcium-dependent manner, by the parathyroid glands. Certain synthetic PTH C-fragments exert actions on %bone% and cartilage cells that are not shared by PTH-(1-34), and specific %binding% of PTH C-%peptides% has been demonstrated in %bone% cells in which PTH1R expression was eliminated by gene targeting. The %peptide% human (h) PTH-(7-84) recently was shown to inhibit the calcemic actions of hPTH-(1-34) or hPTH-(1-84) in parathyroidectomized animals. To determine whether this anticalcemic effect of hPTH-(7-84) in vivo might result from direct actions on %bone%, we studied its effects on both resorption of intact %bone% in vitro and formation of osteoclasts in primary cultures of murine %bone% marrow. Human (h) PTH-(7-84) (300 nM) reduced basal 72-h release of preincorporated 45Ca from neonatal mouse calvariae by 50% (9.6 +- 1.9% vs. 17.8 +- 5.7%; P < 0.001) and similarly inhibited resorption induced by hPTH-(1-84), hPTH-(1-34), 1,25-dihydroxyvitamin D3 (VitD), PGE2, or IL-11. In 12-d murine marrow cultures, both hPTH-(7-84) (300 nM) and hPTH-(39-84) (3000 nM) lowered VitD-dependent formation of osteoclast-like cells by 70%. On the contrary, these actions of hPTH-(7-84) were not observed with the PTH1R antagonists hPTH-(3-34)NH2 and (L11,D-W12,W23,Y36)hPTHrP-(7-36)NH2, which, unlike hPTH-(7-84), did inhibit PTH1R-dependent cAMP accumulation in ROS 17/2.8 cells. We conclude that hPTH-(7-84), acting via receptors distinct from the PTH1R and presumably specific for PTH C-fragments, exerts a direct antiresorptive effect on %bone% that may be partly due to impaired osteoclast differentiation.

2/7/23 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16207446 BIOSIS NO.: 200100379285
Role of %receptor% activator of nuclear factor-kappaB ligand and osteoprotegerin in %bone% cell biology
AUTHOR: Hofbauer Lorenz C (Reprint); Heufelder Armin E
AUTHOR ADDRESS: Division of Gastroenterology, Endocrinology and Metabolism, Zentrum fuer Innere Medizin, Philipps University, 35033, Marburg, Germany **Germany
JOURNAL: Journal of Molecular Medicine (Berlin) 79 (5-6): p243-253 June, 2001 2001
MEDIUM: print
ISSN: 0946-2716
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %Receptor% activator of nuclear factor (NF-kappaB) ligand (RANKL), its cellular %receptor%, %receptor% activator of NF-kappaB (RANK), and the decoy %receptor% osteoprotegerin (OPG) constitute a novel cytokine system. RANKL produced by osteoblastic lineage cells and activated T lymphocytes is the essential factor for osteoclast formation, fusion, activation, and survival, thus resulting in %bone% resorption and %bone% loss. RANKL activates its specific %receptor%, RANK located on osteoclasts and dendritic cells, and its signaling cascade involves stimulation of the c-jun, NF-kappaB, and serine/threonine kinase PKB/Akt pathways. The effects of RANKL are counteracted by OPG which acts as a %soluble% neutralizing %receptor%. RANKL and OPG are regulated by various hormones (glucocorticoids, vitamin D, estrogen), cytokines (tumor necrosis factor alpha, interleukins 1, 4, 6, 11, and 17), and various mesenchymal transcription factors (such as cbfa-1, peroxisome proliferator-activated %receptor% gamma, and Indian hedgehog). Transgenic and knock-out mice with excessive or defective production of RANKL, RANK, and OPG display the extremes of skeletal phenotypes, osteoporosis and osteopetrosis. Abnormalities of the RANKL/OPG system have been implicated in the pathogenesis of postmenopausal osteoporosis, rheumatoid arthritis, Paget's disease, periodontal disease, benign and malignant %bone% tumors, %bone% metastases, and hypercalcemia of malignancy, while administration of OPG has been demonstrated to prevent or mitigate these disorders in animal models. RANKL and OPG are also important regulators of vascular biology and calcification and of the development of a lactating mammary gland during pregnancy, indicating a crucial role for this system in extraskeletal calcium handling. The discovery and characterization of RANKL, RANK, and OPG and subsequent studies have changed the concepts of %bone% and calcium metabolism, have led to a detailed understanding of the pathogenesis of metabolic %bone% diseases, and may form the basis of innovative therapeutic strategies.

2/7/24 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16140076 BIOSIS NO.: 200100311915
Interleukin (IL)-11 upregulates thrombopoietin (Tpo) gene expression and Tpo release by the human stromal cell line, HS27a
AUTHOR: Wu Xiaolin (Reprint); Adamson John W (Reprint)
AUTHOR ADDRESS: The Blood Research Institute, The Blood Center of Southeastern Wisconsin, Milwaukee, WI, USA**USA
JOURNAL: Blood 96 (11 Part 1): p541a November 16, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000; 20001201
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: IL-11 is a stromal cell-derived cytokine with thrombopoietic activity. Alone, IL-11 has only a modest effect on platelet production in vivo but synergizes with other growth factors such as IL-3, IL-6 and Tpo, itself, to promote platelet production in vivo and megakaryocyte (Meg) colony formation in vitro. IL-11 binds directly to Megs and initiates downstream signal transduction events. Nevertheless, we have reported that IL-11 increases Tpo mRNA levels in %bone% marrow stromal cell cultures, and that a Tpo neutralizing antiserum blocks the Meg colony-stimulating activity of IL-11. Others have reported that %soluble% c-mpl (the Tpo %receptor%) blocks the in vitro thrombopoietic activity of IL-11. Thus, at least one mechanism by which IL-11 could affect hematopoiesis is via the upregulation of Tpo gene expression within the marrow microenvironment. To further understand how IL-11 affects Tpo gene expression in the marrow, and the regulatory elements involved, we determined Tpo mRNA levels in stromal cell lines AFT024, HS5 and HS27a using semiquantitative RT-PCR. Only in HS27a cultures were Tpo mRNA levels consistently increased when IL-11 was added (20ng/ml;20-24hr). Using the MTT proliferation assy, we then determined Tpo bioactivity in HS27a conditioned medium (CM) by the growth of UT-7 Tpo, a Tpo-responsive cell line. HS27a CM alone supported UT-7 Tpo growth, but in the presence of a Tpo neutralizing antiserum, cell growth fell by >50%. CM from

IL-11-stimulated HS27a cells increased UT-7 Tpo cell growth by a further 25% - an increase blocked by the antiserum. To study the regulatory mechanisms of Tpo gene expression, we transduced 3 kD of the 5' flanking region of the human Tpo gene (from Kirin Pharmaceutical Co., Japan) into HS27a with a pSEAP reporter system. Using this system, we demonstrated a >2-fold increase in pSEAP activity upon stimulation with IL-11. With serial deletions of the 5' flanking region, we found that bp -2855 to -1842 (from ATG) are critical for the IL-11 response. Computer analysis of this region demonstrated a metallothionein response element (MREd), TGCGC, located at position -2475. This motif is responsible for IL-11-mediated regulation of the proopiomelanocortin gene. Mutation of this motif (to TAAAC) resulted in a 77% reduction in the IL-11 effect on promoter activity in HS27a. Our results show that IL-11 is able to mediate Tpo gene regulation in a functional human stromal cell line through a MREd motif in the Tpo promoter region. IL-11 may exert at least some of its hematopoietic effects in vivo through this mechanism.

2/7/25 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16139994 BIOSIS NO.: 200100311833
Murine hematopoietic stem cell mitogenesis and self-renewal require activation of different cytokine %receptors%
AUTHOR: Audet J (Reprint); Miller C (Reprint); Rose-John S; Piret J; Eaves C (Reprint)
AUTHOR ADDRESS: Terry Fox Laboratory, BC Cancer Agency, Vancouver, BC, Canada**Canada
JOURNAL: Blood 96 (11 Part 1): p493a November 16, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000; 20001201
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have shown that competitive repopulating stem cells (CRU) in normal adult mouse %bone% marrow (BM) can expand their numbers in short term serum-free cultures following activation of 3 cell surface signalling %receptors%: flt3/flk2, c-kit and gp130. In the present study, we examined both the CRU proliferation and self-maintenance response requirements for gp130 activation in single cell and bulk cultures of c-kit+Sca1+lin- mouse BM cells. In 2 experiments, it was observed that Steel factor (SF, 50 ng/mL) and flt3-ligand (FL, 100ng/mL) alone were able to stimulate most of the cells (87% and 88%) to divide within 10 days and the additional presence of either 50 ng/mL interleukin-6 (IL-6) or 40 ng/mL Hyper-IL-6 (H-IL-6, a fusion protein of IL-6 and the %soluble% IL-6 %receptor%) did not increase the number of clones obtained, although the size of the clones increased. Thus gp130 activation was not required for CRU mitogenesis. We next performed a series of H-IL-6 and %interleukin%-%11% (IL-11) dose response experiments in which the yield of CRU at the end of the 10 day culture period was assayed. The results indicated that the addition of 40-100 ng/mL H-IL-6 or 20-100 ng/mL IL-11 (to a base cocktail of 50 ng/mL SF and 100 ng/mL FL) gave maximal expansion of CRU (4-fold) with no net expansion in CRU numbers in the presence of <5 ng/mL H-IL-6 or <2 ng/mL IL-11. Interestingly, the presence of very high concentrations of H-IL-6 or IL-11 (>100 ng/mL) was inhibitory to CRU expansion. These results point to an important and distinct role of gp130-mediated signalling in maintaining hematopoietic stem cell activity and demonstrate for the first time that hematopoietic stem cell mitogenesis and self-renewal can be independently manipulated by the activation of different cell surface cytokine %receptors%.

2/7/26 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16127325 BIOSIS NO.: 200100299164
IL-6 is not an osteogenic differentiation signal for %bone% marrow mesenchymal progenitors
AUTHOR: Erices Alejandro A (Reprint); Conget Paulette A (Reprint); Rojas Cecilia V (Reprint); Minguell Jose J (Reprint)
AUTHOR ADDRESS: Cell Biology, Universidad de Chile, Santiago, Chile**Chile
JOURNAL: Blood 96 (11 Part 2): p118b November 16, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000; 20001201
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Multipotent %bone% marrow mesenchymal progenitors (MPC) are precursors for cells forming several mesenchymal tissues, among them osteoblasts. IL-6-type cytokines (IL-6, IL-11, LIF, OSM) which play a key role in %bone% metabolism, are produced by osteoblasts and exert their biological activity after interacting with specific %receptors% in conjunction with a common transducing element, the membrane protein gp130. In this study we examined whether IL-6 and LIF, influence the proliferation and differentiation of MPC. MPC isolated from normal %bone% marrow harvest were cultured and expanded in alpha-MEM 10% fetal bovine serum, and examined for the production of cytokines, the expression of both membrane and %soluble% specific and common chain %receptors%, and the effect of the cytokines on MPC proliferation and osteogenic differentiation. MPC express mRNAs (ribonuclease protection) for IL-6, LIF, IL-6R, LIFR and gp130. While both cytokines are secreted and detected in the medium (ELISA), MPC express in their membrane gp130, but not IL-6R and LIFR (flow cytometry). In turn, %soluble% gp130 but not %soluble% IL-6R and LIFR were detected (ELISA) in the medium. The incubation of MPC with 20 ng/ml of IL-6 or LIF, alone or with 200 ng/ml of their respective specific %soluble% %receptors%, does not result in a change in cell proliferation. In vitro, MPC differentiation into the osteoblastic lineage is induced by an osteogenic medium (dexamethasone, beta-glycerophosphate, ascorbate), as judged by the time-dependent expression of alkaline phosphatase (AP), Cbfal and osteocalcin (RT-PCR) and by the formation of a mineralized matrix. IL-6 or LIF alone or IL-6 in combination with %soluble% IL-6R, do not mimic the effect of the osteogenic medium. The latter supplemented with IL-6 or LIF results in no changes in the expression of differentiation markers. However, when the osteogenic medium is supplemented with %soluble% IL-6R alone or in combination with IL-6, the onset of osteoblastic differentiation markers, particularly AP, occurs earlier and at a higher magnitude (6-8 fold). These results suggest that the commitment of MPC into the osteoblastic pathway is not modulated by IL-6. However, the terminal maturation of osteogenic committed precursors, is enhanced by IL-6 via %soluble% IL-6R. Thus, in the marrow microenvironment, terminal differentiation of MPC-derived osteogenic precursors, is precluded due to their lack of expression of membrane or %soluble% IL-6R.

2/7/27 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

16042915 BIOSIS NO.: 200100214754
The effect of macrophage-colony stimulating factor and other humoral factors (interleukin-1, -3, -6, and -11, tumor necrosis factor-alpha, and granulocyte macrophage-colony stimulating factor) on human osteoclast formation from circulating cells
AUTHOR: Fujikawa Y; Sabokbar A; Neale S D; Itonaga I; Torisu T; Athanasou N A (Reprint)
AUTHOR ADDRESS: Department of Pathology, Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford, OX3 7LD, UK**UK
JOURNAL: Bone (New York) 28 (3): p261-267 March, 2001 2001

MEDIUM: print
ISSN: 8756-3282
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Macrophage-colony stimulating factor (M-CSF) is an essential requirement for human osteoclast formation, but its effect on the proliferation and differentiation of circulating osteoclast precursor cells is unknown. Other growth factors and cytokines are also known to support/stimulate osteoclast formation from mouse marrow precursors, but it is not certain whether these factors similarly influence human osteoclast formation. In this study, human monocytes were cocultured with osteoblast-like UMR-106 cells on coverslips and dentine slices for up to 21 days in the presence of 1,25 dihydroxyvitamin D3 (10-7 mol/L), dexamethasone (10-8 mol/L), and various concentrations of either M-CSF or other humoral factors (interleukin (IL)-1beta, IL-3, IL-6, and IL-11; tumor necrosis factor-alpha (TNF-alpha); and granulocyte macrophage (GM)-CSF). The effect on osteoclast formation was assessed by tartrate-resistant acid phosphatase (TRAP) and vitronectin %receptor% staining and lacunar %bone% resorption. The results of time-course and proliferation studies showed that M-CSF stimulated both the proliferative and differentiation stages of human osteoclast formation from circulating osteoclast precursors in a dose-dependent manner. A high concentration of M-CSF (100 ng/mL) did not inhibit osteoclast formation. IL-3 and GM-CSF were also capable of stimulating human osteoclast formation, although these growth factors were much less potent than M-CSF.IL-3- and GM-CSF-stimulated osteoclast formation was inhibited by an antibody specific for human M-CSF. Osteoclast formation and lacunar resorption was not seen when either TNF-alpha, IL-1beta, IL-6 (+ %soluble% IL-6 %receptor%), or IL-11 was substituted for M-CSF during coculture. These results confirm that M-CSF is essential for human osteoclast formation from circulating mononuclear precursors, and also shows that IL-3 and GM-CSF may support osteoclast differentiation via the stimulation of M-CSF production by human monocytes.

2/7/28 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14673019 BIOSIS NO.: 199800467266
In vitro expansion of in vivo repopulating hematopoietic stem cells from adult mouse %bone% marrow using HyperIL-6 and its %soluble% %receptor%
AUTHOR: Audet J (Reprint); Miller C L; Rose-John S; Eaves C J; Piret J M
AUTHOR ADDRESS: Biotehcnol. Lab., Univ. British Columbia, Vancouver, BC, Canada**Canada
JOURNAL: Experimental Hematology (Charlottesville) 26 (8): p700 Aug., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 27th Annual Meeting of the International Society for Experimental Hematology Vancouver, British Columbia, Canada August 1-5, 1998; 19980801
SPONSOR: International Society for Experimental Hematology
ISSN: 0301-472X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/29 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13232337 BIOSIS NO.: 199698700170
The cytokines of inflammation
AUTHOR: Cavaillon Jean-Marc
AUTHOR ADDRESS: Unite d'Immuno-Allergie, Inst. Pasteur, 28 rue du Docteur-Roux, 75724 Paris Cedex, France**France
JOURNAL: Comptes Rendus des Seances de la Societe de Biologie et de ses Filiales 189 (4): p531-544 1995 1995
ISSN: 0037-9026
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: French

ABSTRACT: Numerous cytokines are present within inflammatory foci. Interleukin-1 (IL- 1) and tumout necrosis factor (TNF) play a major role in coordinating mechanisms which command inflammation. Upon their action, many different cells produce lipidic mediators, proteolytic enzymes, and free radicals, all directly responsible for the noxious effects observed. IL-1 and TNF exert cytotoxic effects on vascular endothelium, cartilage, %bone% and muscle. Such cytokines as interferon-gamma, IL-3 or granulocyte-macrophage colony stimulating factor amplify the inflammatory response by increasing the production of IL-1 and TNF. The latest trigger the release of chemokines such as IL-8 and macrophage chemoattractant protein-1, the chemotactic activity of which participates in the recruitment of leukocytes within the foci of inflammation. IL-6, abounds in inflammatory processes and induces the production by hepatocytes of acute phase proteins. The same applies to IL-1, TNF, Il-11, the leucocyte inhibitory factor, and the transforming growth factor-beta. The later also processes a number of anti-inflammatory activities and, like IL-4, IL-10 and IL-13, can inhibit IL-1 and TNF production. Such property has also been mentioned for interferon-alpha. These anti-inflammatory cytokines can also counteract some of the IL-1 and TNF activities such as those reported during the coagulation process. Furthermore, these antiinflammatory cytokines can induce the production of the IL-1 %receptor% antagonist which prevents the activities initiated by IL-1. %Soluble% TNF %receptors%, released during inflammation, are the direct inhibitors for TNF. Glucocorticoids, produced following a cascade of events initiated by IL-1, TNF and IL-6, involving the neuroendocrine axis, also inhibit proinflammatory cytokine productions. The concept of "cytokine network" therefore, perfectly illustrates the participation of these mediators in inflammation mechanisms.

2/7/30 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12072647 BIOSIS NO.: 199497093932
Contribution of cytokines to inflammatory processes
AUTHOR: Cavaillon J M
AUTHOR ADDRESS: Unite d'Immune-Allergie, Inst. Pasteur, 28 rue du Dr. Roux, 75015 Paris, France**France
JOURNAL: Pathologie Biologie 41 (8 SUPPL.): p799-811 1993 1993
ISSN: 0369-8114
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: French

ABSTRACT: A large number of cytokines are found within foci of inflammation. Two of these cytokines, namely interleukin-1 (IL-1) and tumor necrosis factor (TNF), play a key role in orchestrating the mechanisms responsible for inflammation. These two cytokines induce production by many cells of lipid mediators, proteases, and free radicals, all of which play a direct role in development of the deleterious effects of inflammation. IL-1 and/or TNF exert cytotoxic effects on the vascular endothelium, cartilage, %bone%, muscle, or pancreatic beta-cell islets. Cytokines, including interferon gamma (IFN), IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), amplify the inflammatory response by increasing production of IL-1 and TNF by macrophages. Macrophages also produce other cytokines, such as IL-8 and macrophage chemoattractant protein-1 (MCP-1), with chemoattractant properties that contribute to draw leucocytes to the site of inflammation. IL-6, produced in large amounts during inflammatory processes, induces the production of acute phase proteins by hepatocytes. IL-1, TNF, IL-11, leukemia inhibitory factor (LIF), and transforming growth factor beta (TGF-beta) share this effect. TGF-beta also has a number of anti-inflammatory effects. TGF-beta, IL-4, and IL-10 inhibit

production of IL-1 and TNF. Glucocorticoids also have this effect. Glucocortioids can be produced as a result of a chain of events initiated by IL-1, TNF, and IL-6 and involving the neuro-endocrine axis. Other substances, such as IL-1 %receptor% antagonist (IL-1 ra) or %soluble% forms of the TNF %receptors%, can specifically inhibit the effects of IL-1 and TNF. Cascade production of cytokines, inhibition, negative feed-back, and synergistic mechanisms are parameters that illustrate the concept of "cytokine network" and aptly characterize the role of these mediators in the mechanisms of inflammation.

2/7/31 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10960490 Genuine Article#: 589QE Number of References: 40
Title: Clonal endothelial cells produce humoral factors that inhibit osteoclast-like cell formation in vitro
Author(s): Chikatsu N; Takeuchi Y (REPRINT) ; Fukumoto S; Yano K; Fujita N; Tsuruo T; Fujita T
Corporate Source: Univ Tokyo,Sch Med, Dept Med, Div Endocrinol,Bunkyo Ku,7-3-1 Hongo/Tokyo 1138655//Japan/ (REPRINT); Univ Tokyo,Sch Med, Dept Med, Div Endocrinol,Bunkyo Ku,Tokyo 1138655//Japan/; Univ Tokyo,Sch Med, Dept Lab Med,Tokyo 1138655//Japan/; Snow Brand Milk Prod Co Ltd,Life Sci Res Inst,Ishibashi/Tochigi 3290512/Japan/; Univ Tokyo,Inst Mol & Cellular Biosci,Tokyo 1130032//Japan/
Journal: ENDOCRINE JOURNAL, 2002, V49, N4 (AUG), P439-447
ISSN: 0918-8959 Publication date: 20020800
Publisher: JAPAN ENDOCRINE SOCIETY, C/O DEPT VETERINARY PHYSIOL, VET MED SCI, UNIV TOKYO, 1-1-1 YAYOI, BUNKYO-KU, TOKYO, 113, JAPAN
Language: English Document Type: ARTICLE
Abstract: Angiogenesis and %bone% remodeling are closely associated, and vascular endothelial cells may have potential roles for osteoclastic %bone% resorption. We examined whether clonal endothelial cells established from %bone%, aorta and brain of Balb/c mice influenced osteoclast-like cell formation in vitro. As low as 1% conditioned media of those endothelial cells inhibited osteoclast-like cell formation in %bone% marrow cultures induced by 1,25-dihydroxyvitamin D-3, and did so in spleen cell cultures in the presence of %soluble% %receptor% activator of nuclear factor-kappaB ligand (RANKL), M-CSF and prostaglandin E-2. The level of osteoprotegerin (OPG), a decoy %receptor% for RANKL, secreted by endothelial cells was not high enough to inhibit osteoclastogenesis. These observations suggest that endothelial cells derived from various tissues secrete factor(s) that inhibits precursors to differentiate into osteoclasts even in the presence of optimal stimulators for osteoclastogenesis. Hence, endothelial cells in %bone% may inhibit recruitment of fresh osteoclasts, and those in tissues other than %bone% may be involved in prohibiting ectopic osteoclastogenesis.

2/7/32 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08230112 Genuine Article#: 260MB Number of References: 27
Title: Hepatocyte growth factor (HGF) induces %interleukin%-%11% secretion from osteoblasts: A possible role for HGF in myeloma-associated osteolytic %bone% disease
Author(s): Hjertner O (REPRINT) ; Torgersen ML; Seidel C; HjorthHansen H; Waage A; Borset M; Sundan A
Corporate Source: NORWEGIAN UNIV SCI & TECHNOL,INST CANC RES & MOL BIOL, MED TEKNISK SENTER/N-7005 TRONDHEIM//NORWAY/ (REPRINT); UNIV HOSP,SECT HEMATOL/TRONDHEIM//NORWAY/
Journal: BLOOD, 1999, V94, N11 (DEC 1), P3883-3888
ISSN: 0006-4971 Publication date: 19991201
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399
Language: English Document Type: ARTICLE
Abstract: Multiple myeloma is associated with unbalanced %bone% remodeling causing lytic %bone% lesions. Interleukin-II (IL-II) promotes osteoclast formation and inhibits osteoblast activity and may, thus, be one factor involved in cancer-induced %bone% destruction. We have previously shown that myeloma cells produce hepatocyte growth factor (HGF). We now report that HGF induces IL-II secretion from human osteoblast-like cells and from the osteosarcoma cell lines Saos-2 and HOS. In coculture experiments, both the myeloma cell line JJN-3 and primary myeloma cells from 3 patients induced IL-II secretion from osteoblasts, whereas no induction was observed with the non-HGF producing myeloma cell line OH-2. Enhanced IL-II induction was observed with physical contact between osteoblasts and myeloma cells as compared with experiments in which contact was prohibited by tissue inserts. Anti-HGF serum strongly reduced the myeloma cell-induced IL-II secretion. Furthermore, we show that JJN-3 cells express HGF on the cell-surface. Removal of surface-bound HGF on JJN-3 cells reduced IL-II production induced in cocultures. Transforming growth factor pi and IL-1 potentiated the effect of HGF on IL-II secretion, whereas an additive effect was observed with tumor necrosis factor. Thus, myeloma-derived HGF can influence the %bone% marrow environment both as a %soluble% and a surface-bound factor. Furthermore, HGF emerges as a possible factor involved in myeloma %bone% disease by its ability to induce IL-11. (C) 1999 by The American Society of Hematology.

2/7/33 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06971963 Genuine Article#: 110EV Number of References: 143
Title: Interleukins in the control of osteoclast differentiation
Author(s): Martin TJ; Romas E; Gillespie MT
Corporate Source: ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/
Journal: CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, 1998, V8, N2, P 107-123
ISSN: 1045-4403 Publication date: 19980000
Publisher: BEGELL HOUSE INC, 79 MADISON AVE, SUITE 1205, NEW YORK, NY 10016-7892
Language: English Document Type: REVIEW
Abstract: To maintain homeostasis of %bone%, the production of osteoblasts and osteoclasts is tightly regulated. At the local level, hormones and cytokines control formation of osteoclasts from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate osteoclast formation by providing physical support and cytokines such as M-CSF and IL-11, which promote osteoclast differentiation. Osteoblasts are also a source of IL-18, which limits osteoclast formation. The require ment of contact between osteoblasts and hemopoietic cells for successful osteoclast formation led to a concept of a membrane-anchored stromal cell molecule that programs osteoclast differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a %soluble% tumor necrosis factor (TNF) family member that inhibits osteoclast formation. The ligand for OPG is a novel transmembrane TNF %receptor% superfamily member, the osteoclast differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of osteoclast differentiation by interleukins.

2/7/34 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06485850 Genuine Article#: YW403 Number of References: 50
Title: Production of %interleukin%-%11% in %bone%-derived endothelial cells and its role in the formation of osteolytic %bone% metastasis
Author(s): Zhang Y; Fujita N; Ohhara T; Morinaga Y; Nakagawa T; Yamada M; Tsuruo T (REPRINT)
Corporate Source: UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU, 1-1-1 YAYOI/TOKYO 113//JAPAN/ (REPRINT); UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU/TOKYO 113//JAPAN/; JAPANESE FDN CANC RES,CTR CANC

CHEMOTHERAPY, TOSHIMA KU/TOKYO 170//JAPAN/
Journal: ONCOGENE, 1998, V16, N6 (FEB 12), P693-703
ISSN: 0950-9232 Publication date: 19980212
Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE, ENGLAND RG21 6XS
Language: English Document Type: ARTICLE
Abstract: The interactions of the cells in the %bone% microenvironment play important roles in %bone% remodeling, Osteoblasts are involved in the %bone% remodeling through the production of %soluble% factors that regulate proliferation and differentiation of osteoclasts and through cell-cell interactions. Histological studies have suggested that endothelial cells are also associated with some osteolytic %bone% diseases, However, it is still unclear how endothelial cells contribute to %bone% resorption, We established %bone%-derived endothelial cells (BDECs) to study their roles in %bone% remodeling, The established BDECs promoted %bone% resorption in a murine neonatal calvaria organ culture system by secreting a %soluble% %bone% resorption-inducing factor(s) when stimulated by several inflammatory cytokines. This %bone% resorption-inducing factor was identified as interleukin-II (IL-11). IL-11 is known to enhance %bone% resorption by promoting osteoclastogenesis and by suppressing the activity of osteoblasts, The production of IL-11 in BDECs was also promoted by conditioned medium of human melanoma A375M cells, Because A375M cells formed osteolytic %bone% metastasis in vivo, BDECs might be involved in pathological osteolysis by producing IL-11, These results suggest that endothelial cells in %bone% play important roles in the promotion of %bone% resorption by secreting IL-11 in physiological and pathological conditions.

2/7/35 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06143991 Genuine Article#: XX869 Number of References: 52
Title: Cytokines to reduce platelet transfusions: Non-TPO cytokines
Author(s): Hamblin T (REPRINT)
Corporate Source: SOUTHAMPTON GEN HOSP,TENOVUS RES LAB, TREMONA RD/SOUTHAMPTON SO16 6YD/HANTS/ENGLAND/ (REPRINT)
Journal: TRANSFUSION SCIENCE, 1997, V18, N1 (MAR), P121-128
ISSN: 0955-3886 Publication date: 19970300
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB
Language: English Document Type: ARTICLE
Abstract: Although thrombopoietin (TPO) has now been cloned, many pretenders have auditioned for the role. It is clear that interleukin-3, interleukin-6, %interleukin%-%11%, stem cell factor, leukaemia inhibitory factor and oncostatin-M all influence the proliferation and maturation of megakaryocytes. This review details the nature of these non-TPO cytokines, giving their genetic identity, molecular structure, %receptor%, mode of action and range of activities. Their effect on platelet production in preclinical and clinical studies is reported and their potential as agents for thrombopoietic support is discussed. (C) 1997 Elsevier Science Ltd.

2/7/36 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05787934 Genuine Article#: WX516 Number of References: 337
Title: Interleukin-6: Structure-function relationships
Author(s): Simpson RJ (REPRINT) ; Hammacher A; Smith DK; Matthews JM; Ward LD
Corporate Source: ROYAL MELBOURNE HOSP,LUDWIG INST CANC RES, POB 2008/MELBOURNE/VIC 3050/AUSTRALIA/ (REPRINT); WALTER & ELIZA HALL INST MED RES,/PARKVILLE/VIC 3050/AUSTRALIA/; LUDWIG INST CANC RES,MELBOURNE TUMOUR BIOL BRANCH, JOINT PROT STRUCT LAB/PARKVILLE/VIC 3050/AUSTRALIA/ ; COOPERAT RES CTR CELLULAR GROWTH FACTORS,/PARKVILLE/VIC 3050/AUSTRALIA/
Journal: PROTEIN SCIENCE, 1997, V6, N5 (MAY), P929-955
ISSN: 0961-8368 Publication date: 19970500
Publisher: CAMBRIDGE UNIV PRESS, 40 WEST 20TH STREET, NEW YORK, NY 10011-4211
Language: English Document Type: REVIEW
Abstract: Interleukin-6 (IL-6) is a multifunctional cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities and its potent ability to induce the acute phase response. Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis, and post-menopausal osteoporosis. Hence, selective antagonists of IL-6 action may offer therapeutic benefits. IL-6 is a member of the family of cytokines that includes %interleukin%-%11%, leukemia inhibitory factor, oncostatin M, cardiotrophin-1 and ciliary neurotrophic factor. Like the other members of this family, IL-6 induces growth or differentiation via a %receptor%-system that involves a specific %receptor% and the use of a shared signaling subunit, gp130. Identification of the regions of IL-6 that are involved in the interactions with the IL-6 %receptor% and gp130 is an important first step in the rational manipulation of the effects of this cytokine for therapeutic benefit. In this review, we focus on the sites on IL-6 which interact with its low-affinity specific %receptor%, the IL-6 %receptor%, and the high-affinity converter gp130. A tentative model for the IL-6 hexameric %receptor% ligand complex is presented and discussed with respect to the mechanism of action of the other members of the IL-6 family of cytokines.

2/7/37 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2007 The Thomson Corp. All rts. reserv.

05351618 Genuine Article#: VR973 Number of References: 42
Title: MOLECULAR-CLONING AND CHARACTERIZATION OF MURINE %INTERLEUKIN%-%11%
Author(s): MORRIS JC; NEBEN S; BENNETT F; FINNERTY H; LONG A; BEIER DR; KOVACIC S; MCCOY JM; DIBLASIOSMITH E; LAVALLIE ER; CARUSO A; CALVETTI J ; MORRIS G; WEICH N; PAUL SR; CROSIER PS; TURNER KJ; WOOD CR
Corporate Source: GENET INST INC,87 CAMBRIDGE PK DR/CAMBRIDGE//MA/02140; GENET INST INC/CAMBRIDGE//MA/02140; BRIGHAM & WOMENS HOSP,DIV GENET/BOSTON//MA/02115; BROWN UNIV,SCH MED,DEPT PEDIAT/PROVIDENCE//RI/02912; UNIV AUCKLAND,DEPT MOL MED/AUCKLAND 1//NEW ZEALAND/
Journal: EXPERIMENTAL HEMATOLOGY, 1996, V24, N12 (OCT), P1369-1376
ISSN: 0301-472X
Language: ENGLISH Document Type: ARTICLE
Abstract: Human %interleukin%-%11% (IL-11) has been shown to have pleiotropic action on hematopoietic, hepatic, stromal, epithelial, neural, and osteoclast cells. In the present work, the murine IL-11 cDNA has been isolated from a fetal thymic cell line, and its structure and function compared with human IL-11. The murine protein was demonstrated to have identical actions on the proliferation of a murine plasmacytoma cell line, murine primitive %bone% marrow progenitor cells, and megakaryocyte precursors. The murine IL-11 protein was syn thesized as a %soluble% thioredoxin-IL-11 fusion in Escherichia coli and the expression of murine IL-11 was examined by pulse-chase radiolabeling in COS cells. The chromosomal location of the murine IL-11 gene was assigned to the proximal arm of chromosome 7.

2/7/38 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2007 The Thomson Corp. All rts. reserv.

04925689 Genuine Article#: UT086 Number of References: 50
Title: %INTERLEUKIN%-%11% MESSENGER-RNA STABILIZATION IN PHORBOL ESTER-STIMULATED PRIMATE %BONE%-MARROW STROMAL CELLS
Author(s): YANG L; STEUSSY CN; FUHRER DK; HAMILTON J; YANG YC
Corporate Source: INDIANA UNIV,SCH MED,WALTHER ONCOL CTR,975 W WALNUT ST,IB 540/INDIANAPOLIS//IN/46202; INDIANA UNIV,SCH MED,WALTHER ONCOL

CTR/INDIANAPOLIS//IN/46202; INDIANA UNIV,SCH MED,DEPT MED HEMATOL ONCOL/INDIANAPOLIS//IN/46202; INDIANA UNIV,SCH MED,DEPT BIOCHEM & MOLEC BIOL/INDIANAPOLIS//IN/46202
Journal: MOLECULAR AND CELLULAR BIOLOGY, 1996, V16, N7 (JUL), P3300-3307
ISSN: 0270-7306
Language: ENGLISH Document Type: ARTICLE
Abstract: 12-O-Tetradecanoylphorbol-13-acetate (TPA) stimulation of PU-34,cells, a primate hone marrow stromal cell line, resulted in a prolonged elevation of %interleukin%-%11% (IL-11)-mRNA, which can be inhibited by protein synthesis inhibitors, Nuclear run-on assays and actinomycin D experiments demonstrated that the up-regulation of IL-11 gene expression is mainly controlled at the posttranscriptional level through the protein kinase C (PKC) pathway. Inhibition of PRC activity by calphostin C generated an IL-11 mRNA degradation intermediate in TPA-stimulated PU-34 cells. This intermediate retains the 5' untranslated region (5'UTR) and coding region of the IL-11 mRNA but has lost the poly(A) tail add the 3'UTR. The mechanisms underlying IL-11 mRNA stabilization were further investigated by transfections with a variety of chimeric IL-11 constructs and deletion mutants, Two important observations were made from these transient expression experiments: (i) the same 3'UTR of IL-11 mRNA shown to confer instability in one chimeric transcript may not function as a destabilizer in another chimeric RNA, and (ii) the 5'UTR, coding region, and 3'UTR all contribute to IL-11 mRNA decay, and labile IL-11 deletion transcripts are not necessarily stabilized by TPA stimulation, Our study suggests that multiple regions within the IL-11 mRNA are involved in TPA-stimulated IL-11 mRNA stabilization, possibly through a unique RNA folding conformation involving interactions of various RNA sequences within the IL-11 mRNA molecule.

2/7/39 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04584512 Genuine Article#: TV597 Number of References: 72
Title: THE HUMAN IL-11 %RECEPTOR% REQUIRES GP130 FOR SIGNALING - DEMONSTRATION BY MOLECULAR-CLONING OF THE %RECEPTOR%
Author(s): NANDURKAR HH; HILTON DJ; NATHAN P; WILLSON T; NICOLA N; BEGLEY CG
Corporate Source: ROYAL MELBOURNE HOSP,WALTER & ELIZA HALL INST MED RES/MELBOURNE/VIC 3050/AUSTRALIA/; ROYAL MELBOURNE HOSP,COOPERAT RES CTR CELLULAR GROWTH FACTORS/MELBOURNE/VIC 3050/AUSTRALIA/; ROYAL MELBOURNE HOSP,ROTARY BONE MARROW RES LAB/MELBOURNE/VIC 3050/AUSTRALIA
Journal: ONCOGENE, 1996, V12, N3 (FEB 1), P585-593
ISSN: 0950-9232
Language: ENGLISH Document Type: ARTICLE
Abstract: We describe the molecular cloning of a cDNA for the alpha chain of the human IL-11 %receptor% (IL-11R alpha) and demonstrate the requirement of either the human or mouse gp130 molecule for signalling. cDNA clones encoding IL-11R alpha were isolated from a %bone% marrow cDNA library using a fragment from the murine IL-11R alpha as a probe, The human %receptor% was predicted to consist of 422 amino acids and was found to share 84% identity with the murine protein. In the extra-cellular region it exhibited a single hemopoietin domain with conserved cysteine residues and WSTWS motif. The transmembrane region was followed by a short cytoplasmic tail which did not contain a tyrosine kinase domain. Interaction of the human IL-11R alpha with murine gp130 was demonstrated: expression of the human IL-11R alpha in murine M1 cells which constitutively express murine gp130 (and murine LIF %receptor%), resulted in the generation of specific high-affinity binding sites for IL-11 (K-d=250 pM). In addition, expression of the human IL-11R alpha in these cells permitted the induction of macrophage differentiation in response to IL-11, These results suggested that the human IL-11R alpha chain was able to form a functional %receptor% complex in association with murine gp130. The requirement of gp130 for signalling was confirmed by expression of the human IL-11R alpha in Ba/F3 cells. BaF3 cells that expressed the human IL-11R alpha alone showed binding of radiolabelled IL-11 but no proliferative response. Introduction of human gp130 into these cells resulted in high-affinity IL-11 binding sites and IL-11 dependent cellular proliferation. Thus these results demonstrated the absolute requirement of gp130 for signalling.

2/7/40 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04411515 Genuine Article#: TB894 Number of References: 64
Title: INTERLEUKIN (IL)-6 INDUCTION OF OSTEOCLAST DIFFERENTIATION DEPENDS ON IL-6 %RECEPTORS% EXPRESSED ON OSTEOBLASTIC CELLS BUT NOT ON OSTEOCLAST PROGENITORS
Author(s): UDAGAWA N; TAKAHASHI N; KATAGIRI T; TAMURA T; WADA S; FINDLAY DM ; MARTIN TJ; HIROTA H; TADA T; KISHIMOTO T; SUDA T
Corporate Source: SHOWA UNIV,SCH DENT,DEPT BIOCHEM,SHINAGAWA KU,1-5-8 HATANODAI/TOKYO 142//JAPAN/; SHOWA UNIV,SCH DENT,DEPT BIOCHEM,SHINAGAWA KU/TOKYO 142//JAPAN/; UNIV MELBOURNE,ST VINCENTS INST MED RES/FITZROY/VIC 3065/AUSTRALIA/; OSAKA UNIV,SCH MED,DEPT MED 3/OSAKA 565//JAPAN/; OSAKA UNIV,INST MOLEC & CELL BIOL/OSAKA 565//JAPAN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1995, V182, N5 (NOV 1), P 1461-1468
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE
Abstract: We reported that interleukin (IL) 6 alone cannot induce osteoclast formation in cocultures of mouse %bone% marrow and osteoblastic cells, but %soluble% IL-6 %receptor% (IL-6R) strikingly triggered osteoclast formation induced by IL-6. In this study, we examined the mechanism of osteoclast formation by IL-6 and related cytokines through the interaction between osteoblastic cells and osteoclast progenitors. When dexamethasone was added to the cocultures, IL-6 could stimulate osteoclast formation without the help of %soluble% IL-6R. Osteoblastic cells expressed a very low level of IL-6R mRNA, whereas fresh mouse spleen and %bone% marrow cells, both of which are considered to be osteoclast progenitors, constitutively expressed relatively high levels of IL-6R mRNA. Treatment of osteoblastic cells with dexamethasone induced a marked increase in the expression of IL-6R mRNA. By immunoblotting with antiphosphotyrosine antibody, IL-6 did not tyrosine-phosphorylate a protein with a molecular mass of 130 kD in osteoblastic cells but did so in dexamethasone-pretreated osteoblastic cells. Osteoblastic cells from transgenic mice constitutively expressing human IL-6R could support osteoclast development in the presence of human IL-6 alone in cocultures with normal spleen cells. In contrast, osteoclast progenitors in spleen cells from transgenic mice overexpressing human IL-6R were not able to differentiate into osteoclasts in response to IL-6 in cocultures with normal osteoblastic cells. These results clearly indicate that the ability of IL-6 to induce osteoclast differentiation depends on signal transduction mediated by IL-6R expressed on osteoblastic cells but not on osteoclast progenitors.

2/7/41 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04121861 Genuine Article#: RG973 Number of References: 67
Title: ACTIVATION OF B-LYMPHOCYTE MATURATION BY A HUMAN FOLLICULAR DENDRITIC CELL-LINE, FDC-1
Author(s): CLARK EA; GRABSTEIN KH; GOWN AM; SKELLY M; KAISHO T; HIRANO T; SHU GL
Corporate Source: UNIV WASHINGTON,MED CTR,DEPT MICROBIOL,SC-42/SEATTLE//WA/98195; UNIV WASHINGTON,MED CTR,DEPT PATHOL/SEATTLE//WA/98195; UNIV WASHINGTON,MED CTR,REG PRIMATE RES CTR/SEATTLE//WA/98195; IMMUNEX CORP/SEATTLE//WA/98101; OSAKA UNIV,SCH MED,BIOMED RES CTR,DIV MOLEC ONCOL/OSAKA 553//JAPAN/
Journal: JOURNAL OF IMMUNOLOGY, 1995, V155, N2 (JUL 15), P545-555
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: Previously, we described the characteristics of a cell line that

is derived from a low density fraction of human tonsillar cells and, on the basis of a number of criteria, is related to follicular dendritic cells (FDC). This line, FDC-1, binds B lymphocytes and not T lymphocytes, and promotes anti-Ig- or anti-CD40-induced B cell proliferation. In this work, we show that culturing B cells with small numbers of FDC-1 cells leads to significant production of IL-6 and of both IgM and IgG. As few as 50 to 100 FDC-1 augmented B cell IgM production by 10- to 100-fold. Although fixed FDC-1 cells, unlike live FDC-1 cells, do not stimulate Ig production, cell contact is not required for all FDC-dependent Ig production. Supernatants from cultured FDC-1. cells can also stimulate B cells to produce IgM, suggesting that FDC produce a %soluble% B cell stimulating factor(s). Augmentation of FDC-dependent IgM production by either IL-6 or IL-7 and augmentation of FDC-dependent IgG production by IL-4 does require FDC-1 cells to be in contact with B cells. When the effects of FDC-1 cells were compared with those of epithelial cell lines and human foreskin fibroblasts (HFF), both FDC-1 cells and HFF induced B cells to produce IgM. FDC-1, unlike HFF, were positive for CD40, CD54, CD73, CD74, and nerve growth factor %receptor% (NGFR), and unlike HFF, but like certain stromal cells, FDC-1 cells also expressed smooth muscle actin, and a novel marker for stromal cells, BST-1. The possible relationship of FDC-1 cells and FDC in general to a fibroblast/stromal cell lineage is discussed.

2/7/42 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04084509 Genuine Article#: RD188 Number of References: 39
Title: STEM-CELL FACTOR IN APLASTIC-ANEMIA - IN-VITRO EXPRESSION IN %BONE% -MARROW STROMA AND FIBROBLAST-CULTURES
Author(s): KRIEGER MS; NISSEN C; WODNARFILIPOWICZ A
Corporate Source: UNIV BASEL HOSP,DEPT RES,HEBELSTR 20/CH-4031 BASEL//SWITZERLAND/; UNIV BASEL HOSP,DEPT RES/CH-4031 BASEL//SWITZERLAND/; UNIV BASEL HOSP,DEPT CLIN HEMATOL/CH-4031 BASEL//SWITZERLAND/
Journal: EUROPEAN JOURNAL OF HAEMATOLOGY, 1995, V54, N4 (APR), P262-269
ISSN: 0902-4441
Language: ENGLISH Document Type: ARTICLE
Abstract: In vitro expression of stem-cell factor (SCF) by %bone% marrow (BM) cells of 30 patients with aplastic anemia (AA) has been analyzed at the mRNA and protein levels. While no deficiencies were found in SCF mRNA expression, low levels of %soluble% SCF protein were measured in poorly growing AA stroma cultures. The SCF protein concentration in the supernatant and the confluence of AA stroma growth were found to correlate (R = 0.70). Defective proliferation was observed in the majority (20/30) of AA stroma cultures and was paralleled by poor growth of homogeneous cultures of fibroblasts from the same marrow sample. AA stroma growth was enhanced by addition of exogenous SCF in combination with %interleukin%-%11% (IL-11), leukemia inhibitory factor (LIF), and basic fibroblast growth factor (bFGF). Our results demonstrate that deficient growth of stroma cells results in decreased production of SCF. Therefore, SCF and other stroma-derived cytokines may be of therapeutic value in BA patients with documented defects within the BM microenvironment.

2/7/43 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04007022 Genuine Article#: QY617 Number of References: 357
Title: HODGKINS-DISEASE - A CYTOKINE-PRODUCING TUMOR - A REVIEW
Author(s): GRUSS HJ; HERRMANN F; DREXLER HG
Corporate Source: FREE UNIV BERLIN,KLINIKUM RUDOLF VIRCHOW,MAX DELBRUCK CTR MOLEC MED,ROBERT ROSSLE CANC CTR/D-13122 BERLIN//GERMANY/; MAX DELBRUCK CTR MOLEC MED/BERLIN//GERMANY/; GERMAN COLLECT MICROORGANISMS & CELL CULTURES/BRAUNSCHWEIG//GERMANY/; IMMUNEX RES & DEV CORP/SEATTLE//WA/98101
Journal: CRITICAL REVIEWS IN ONCOGENESIS, 1994, V5, N5, P473-538
ISSN: 0893-9675
Language: ENGLISH Document Type: REVIEW
Abstract: Cytokines and hematopoietic growth factors are actively involved in regulation of proliferation, differentiation, and cellular functions of various cell lineages. Each cytokine exhibits pleiotropic biological functions on different target cells acid subfamilies of cytokines often have redundant biological effects on the same target cell. Hodgkin's disease represents one of the most common human lymphoma entities, the molecular pathogenesis of which is not well understood. Hodgkin's disease is characterized by the presence of typical, presumed malignant Hodgkin and Reed-Sternberg cells in a hyperplastic background of normal reactive lymphocytes, plasma cells, histiocytes, neutrophils, eosinophils, and stromal cells. The histopathological presentation and characteristic clinical features of Hodgkin's disease correlate with an unbalanced production of multiple cytokines. Hodgkin and Reed-Sternberg cells express mRNA and proteins of various cytokines, growth factors, and cytokine %receptors%, implying a predominant role for cytokines in the pathophysiology of Hodgkin's disease as a tumor of cytokine-producing cells.

2/7/44 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03822177 Genuine Article#: QJ435 Number of References: 32
Title: LONG-TERM CULTURE OF CHRONIC MYELOGENOUS LEUKEMIA MARROW-CELLS ON STEM-CELL FACTOR-DEFICIENT STROMA FAVORS BENIGN PROGENITORS
Author(s): AGARWAL R; DOREN S; HICKS B; DUNBAR CE
Corporate Source: NHLBI,HEMATOL BRANCH,BLDG 10,ROOM 7C103,9000 ROCKVILLE PIKE/BETHESDA//MD/20892; NHLBI,HEMATOL BRANCH/BETHESDA//MD/20892; CHILDRENS HOSP,MED CTR/CINCINNATI//OH/45229
Journal: BLOOD, 1995, V85, N5 (MAR 1), P1306-1312
ISSN: 0006-4971
Language: ENGLISH Document Type: ARTICLE
Abstract: Long-term culture of marrow from patients with chronic myelogenous leukemia (CML) has been reported to favor the outgrowth of bcr/abl(-) progenitor cells in some patients. We examined the effect of the presence of %soluble% or transmembrane forms of stem cell factor (SCF) in long-term cultures of CML marrow. CD34-enriched cells from CML patients in advanced chronic phase or accelerated phase were plated on immortalized fetal liver stromal cells from homozygous SCF-deficient Sl/Sl mice (Sl/Sl(4)) with or without the addition of %soluble% human SCF, Sl/Sl(4) cells expressing high levels of the transmembrane form of human SCF (Sl/Sl(h220)), or primary human allogeneic stroma. Cells were removed from cultures and plated weekly in colony assays. The clonagenic cell output from cultures completely lacking SCF was lower over the first 2 to 3 weeks, but by 5 weeks was similar to the clonagenic cell output from the other culture conditions. Analysis of bcr/abl transcripts from individual colonies showed a lower percentage of malignant progenitors present in long-term cultures completely deficient in SCF than under the other culture conditions, particularly compared with primary human stroma-containing long-term cultures. SCF may specifically favor malignant versus benign progenitor cells present in the marrow of CML patients, and an abnormal proliferative response to SCF in very primitive cells may be an underlying defect in the pathophysiology of this disease.

2/7/45 (Item 15 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03804929 Genuine Article#: QG770 Number of References: 46
Title: EXPRESSION CLONING OF CARDIOTROPHIN-1, A CYTOKINE THAT INDUCES CARDIAC MYOCYTE HYPERTROPHY
Author(s): PENNICA D; KING KL; SHAW KJ; LUIS E; RULLAMAS J; LUOH SM; DARBONNE WC; KNUTZON DS; YEN R; CHIEN KR; BAKER JB; WOOD WI
Corporate Source: GENENTECH INC,DEPT BIOL MOLEC,460 POINT SAN BRUNO BLVD/S

SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT CARDIOVASC RES/S SAN FRANCISCO//CA/94080; GENENTECH INC,DEPT BIOANALYT TECHNOL/S SAN FRANCISCO//CA/94080; UNIV CALIF SAN DIEGO,AMER HEART ASSOC,BUGHER FDN CTR MOLEC BIOL,DEPT MED/LA JOLLA//CA/92093; UNIV CALIF SAN DIEGO,CTR GENET MOLEC/LA JOLLA//CA/92093
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1995, V92, N4 (FEB 14), P1142-1146
ISSN: 0027-8424
Language: ENGLISH Document Type: ARTICLE
Abstract: Heart failure continues to be a leading cause of mortality worldwide. A hallmark of this disease is dilated cardiac hypertrophy, which is accompanied by a reactivation of genes expressed in fetal heart development. Reasoning that fetal or embryonic growth factors may mediate the onset of cardiac hypertrophy, we have coupled expression cloning with an embryonic stem cell-based model of cardiogenesis to isolate a 21.5-kDa protein, cardiotrophin 1, that potently induces cardiac myocyte hypertrophy in vitro. Amino acid similarity data indicate that cardiotrophin 1 is a member of the leukemia inhibitory factor/ciliary neurotrophic factor/oncostatin M/interleukin 6/ %interleukin% %11% family of cytokines. Several members of this family that are known to signal through the transmembrane protein gp130 stimulate cardiac myocyte hypertrophy, like cardiotrophin 1, suggesting that the gp130 signaling pathway may play a role in cardiac hypertrophy. A 1.4-kb cardiotrophin 1 mRNA is expressed in the heart and several other mouse tissues.

2/7/46 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03791605 Genuine Article#: QF604 Number of References: 37
Title: PRECLINICAL SAFETY STUDIES WITH RECOMBINANT HUMAN INTERLEUKIN-6 (RHIL-6) IN THE PRIMATE CALLITHRIX-JACCHUS (MARMOSET) - COMPARISON WITH STUDIES IN RATS
Author(s): RYFFEL B; WEBER M
Corporate Source: UNIV ZURICH,INST TOXICOL/CH-8603 SCHWERZENBACH//SWITZERLAND/
Journal: JOURNAL OF APPLIED TOXICOLOGY, 1995, V15, N1 (JAN-FEB), P19-26
ISSN: 0260-437X
Language: ENGLISH Document Type: ARTICLE
Abstract: The haemopoietic and immunostimulatory properties of recombinant human interleukin 6 (rhIL-6) might be used clinically in cancer patients. For the preclinical assessment of the safety of such a therapy, we chose the primate marmoset (Callithrix jacchus) and Wistar rats.

Recombinant hIL-6 given to marmosets at doses of up to 1000 mu g kg(-1) day(-1) over 4 and 9 weeks did not induce fever and was very well tolerated. Haematological alterations included a sustained two- to threefold increase of thrombocyte counts, peaking at 4 weeks, as well as an increase in neutrophils and basophils. The number of %bone% marrow megakaryocytes at 4 and 9 weeks was not increased, but the ploidy grade was augmented. An acute-phase protein response was observed within 24 h after the first IL-6 administration, which reached a maximum after 1 week. The acute-phase protein response was not accompanied by functional or morphological signs of hepatocellular damage. Increased immunoglobulin and %soluble% IL-2 %receptor% in the serum levels reflected systemic immunostimulation.

Recombinant hIL-6 was also given to rats at 500 mu g kg(-1) day(-1) s.c. for 4 weeks, where it induced a stimulation of thrombopoiesis associated with increased platelet counts within 1 week. Furthermore, rhIL-6-treated rats had signs of immunostimulation and increased acute-phase reactants in serum, as in marmosets. There was no evidence of renal glomerular or hepatic pathology.

In conclusion, despite the pleiotrophic effects of IL-6 observed lip vitro, prolonged administration of rhIL-6 induced quite a selective stimulation of thrombopoiesis and the immune system, which were not associated with any major adverse effect in the two animal species. Since neutralizing antibodies developed against rhIL-6 in both species within 2-4 weeks, which abolished the biological effect of IL-6, the conductance of long-term studies with rhIL-6-especially on possible tumour-promoting effects-are not warranted.

2/7/47 (Item 17 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03771027 Genuine Article#: QD586 Number of References: 53
Title: CYTOKINE AND HORMONAL-STIMULATION OF HUMAN OSTEOSARCOMA %INTERLEUKIN%-%11% PRODUCTION
Author(s): ELIAS JA; TANG WL; HOROWITZ MC
Corporate Source: YALE UNIV,SCH MED,DEPT INTERNAL MED,PULM CRIT CARE MED SECT,333 CEDAR ST,1105 LCI/NEW HAVEN//CT/06250; YALE UNIV,SCH MED,DEPT ORTHOPED & REHABIL/NEW HAVEN//CT/06250; VET ADM MED CTR,RES SERV/W HAVEN//CT/06516
Journal: ENDOCRINOLOGY, 1995, V136, N2 (FEB), P489-498
ISSN: 0013-7227
Language: ENGLISH Document Type: ARTICLE
Abstract: Osteoclast-mediated %bone% resorption plays a crucial role in osseous remodeling. Osteoblasts are important regulators of this activity, in part through their ability to produce osteoclast-regulating %soluble% factors such as interleukin-6 (IL-6). IL-11 is a newly appreciated pleotropic cytokine whose spectrum of biological activities overlaps with that of IL-6. As a result, we hypothesized that osteoblasts are an important skeletal source of this cytokine. To test this hypothesis, we characterized the IL-11 production of unstimulated and stimulated SaOS-2 human osteosarcoma cells. Unstimulated cells produced modest amounts of IL-11. The osteotropic agents recombinant IL-1 (0.25-5 ng/ml), transforming growth factor-beta 1 (0.1-10 ng/ml), PTH (10(-8)-10(-11) M), and PTH-related peptide (10(-8)-10(-11) M) further increased SaOS-2 cell IL-11 protein production and messenger RNA accumulation. These stimulatory effects were dose and time dependent, and the IL-11 that was produced was bioactive, as demonstrated by its ability to stimulate the proliferation of T10D plasmacytoma cells. The protein kinase-C activator, 12-O-Tetra-decanoylphorbol 13-acetate, and a variety of cAMP agonists [forskolin, prostaglandin E(1), prostaglandin E(2), and (Bu)(2)AMP] also stimulated osteoblast IL-11 protein production and messenger RNA accumulation. In contrast, recombinant IL-4, recombinant interferon-gamma, and endotoxin did not stimulate SaOS-2 cells in a similar fashion. Importantly, the ability to produce IL-11 was not a unique property of SaOS-2 cells, because primary human trabecular %bone% osteoblasts also produced significant amounts of bioactive IL-11 when stimulated with transforming growth factor-beta 1. These studies demonstrate that appropriately stimulated human osteoblasts and osteoblast-like cells are potent producers of IL-11 and suggest that osteoblast-derived IL-11 may be an important component of the cytokine network mediating osteoblast-osteoclast communication in normal and pathological %bone% remodeling.

2/7/48 (Item 18 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03689826 Genuine Article#: PY200 Number of References: 134
Title: HEMATOPATHOLOGY OF INTERLEUKIN 6-TYPE CYTOKINES
Author(s): HAWLEY RG
Corporate Source: UNIV TORONTO,SUNNYBROOK HLTH SCI CTR,DIV CANC RES,2075 BAYVIEW AVE/TORONTO/ON M4N 3M5/CANADA/; UNIV TORONTO,DEPT MED BIOPHYS/TORONTO/ON/CANADA/
Journal: STEM CELLS, 1994, V12, S1, P155-171
ISSN: 1066-5099
Language: ENGLISH Document Type: REVIEW
Abstract: Interleukin (IL)-6, IL-11, leukemia inhibitory factor (LIF), oncostatin EM (OSM) and ciliary neurotrophic factor (CNTF) constitute a

subfamily of cytokines on the basis of similar predicted structures and functional redundancy in their actions on a wide spectrum of cell types. Among the diverse targets of these pleiotropic factors are adipocytes, embryonic stem cells, hepatocytes, and cells belonging to the hematopoietic, immune and nervous systems. An explanation for the shared biologic activities of IL-6 subfamily members is provided by the finding that these cytokines trigger overlapping signal transduction pathways in responsive cells through a common %receptor% submit, termed gp130. With the exception of CNTF, which appears to function primarily within the nervous system, IL-6-type cytokines differ from classical hormones in that they are synthesized by many tissues, frequently in association with disease states or in response to infection or injury. This article discusses the hematologic effects of dysregulated expression of IL-6 and related cytokines, highlighting results obtained in our laboratory with murine models of cytokine excess created by retroviral gene delivery to the hematopoietic system.

2/7/49 (Item 19 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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02881050 Genuine Article#: MM515 Number of References: 36
Title: %SOLUBLE% INTERLEUKIN-6 %RECEPTOR% TRIGGERS OSTEOCLAST FORMATION BY INTERLEUKIN-6
Author(s): TAMURA T; UDAGAWA N; TAKAHASHI N; MIYAURA C; TANAKA S; YAMADA Y; KOISHIHARA Y; OHSUGI Y; KUMAKI K; TAGA T; KISHIMOTO T; SUDA T
Corporate Source: SHOWA UNIV,SCH DENT,DEPT BIOCHEM,1-5-8 HATANODAI,SHINAGAWA KU/TOKYO 142//JAPAN/; SHOWA UNIV,SCH DENT,DEPT BIOCHEM,1-5-8 HATANODAI,SHINAGAWA KU/TOKYO 142//JAPAN/; OSAKA UNIV,INST MOLEC & CELLULAR BIOCHEM/OSAKA//JAPAN/; CHUGAI PHARMACEUT CO LTD,FUJI GOTEMBA RES LABS/SHIZUOKA 412//JAPAN/; OSAKA UNIV,SCH MED,DEPT MED 3/SUITA/OSAKA 565/JAPAN/
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 1993, V90, N24 (DEC 15), P11924-11928
ISSN: 0027-8424
Language: ENGLISH Document Type: ARTICLE
Abstract: It has been reported that %soluble% interleukin (IL)-6 %receptor% (sIL-6R) is detected in the serum of healthy individuals and its level is increased in patients with multiple myeloma and human immunodeficiency virus infection. Although several reports have suggested that sIL-6R potentiates IL-6 action, its physiological role remains unclear. In this study, we examined the role of sIL-6R on osteoclast formation by IL-6, using a coculture of mouse osteoblasts and %bone% marrow cells. Neither recombinant mouse IL-6 (mIL-6) nor mouse sIL-6R (smIL-6R) induced osteoclast-like multinucleated cell (MNC) formation when they were added separately. In contrast, simultaneous treatment with mIL-6 and smIL-6R strikingly induced MNC formation. These MNCs satisfied major criteria of authentic osteoclasts, such as tartrate-resistant acid phosphatase (TRAP) activity, calcitonin %receptors%, and pit formation on dentine slices. The MNC formation induced by mIL-6 and smIL-6R was dose-dependently inhibited by adding monoclonal anti-mouse IL-6R antibody (MR16-1). It is likely that osteoblasts and osteoclast progenitors are capable of transducing a signal from a complex of IL-6 and sIL-6R through gp130, even though they may have no or a very small number of IL-6Rs. Factors such as IL-11, oncostatin M, and leukemia inhibitory factor, which are known to exert their functions through gp130 (the signal-transducing chain of IL-6R), also induced MNC formation in our coculture system. These results suggest that increased circulating or locally produced sIL-6R induces osteoclast formation in the presence of IL-6 mediated by a mechanism involving gp130. This may play an important physiological or pathological role in conditions associated with increased osteoclastic %bone% resorption.

2/7/50 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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13931893 EMBASE No: 2006328252
Biological therapies for inflammatory bowel disease: Research drives clinics
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Mini-Reviews in Medicinal Chemistry (MINI-REV. MED. CHEM.) (Netherlands) 2006, 6/7 (771-784)
CODEN: MMCIA ISSN: 1389-5575
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 138

The better understanding of the mechanisms of inflammatory bowel disease has driven our progress into the development of new biological therapies targeting specific molecules. Anti-TNF-alpha biologic compounds have shown great efficacy particularly in Crohn's disease. Infliximab (an IgG1 mouse/human chimeric monoclonal anti-TNF-alpha antibody fragment) is the most efficacious compound in induction and maintenance therapy of active and fistulizing Crohn's disease, being at present the only biological compound approved for therapy, but with the limit of the immunogenicity; CDP571 (a humanized anti-TNF-alpha antibody) and CDP-870 (a PEGylated anti-TNF-alpha antibody) are less immunogenic, showed some efficacy in induction therapy in Crohn's disease but a rapid loss of response in maintenance therapy. Etanercept and onercept (%soluble% human recombinant TNF-alpha %receptors% fusion proteins) seem not to be efficacious in Crohn's disease demonstrating no class-effect for anti-TNF-alpha compounds. In preliminary study, adalimumab (an IgG1 humanized monoclonal anti-TNF-alpha antibody) offers good perspective of efficacy and safety also in infliximab-resistant or allergic patients. Inhibition of lymphocyte trafficking to the gut, through anti-adhesion molecules specific therapies (natalizumab, MLN-02, alicaforsen), has shown promising results: unfortunately, natalizumab, the most effective drug of this class, has recently been suspected to favour serious neurological complications. Other biologic therapies are under evaluation but at present seem to be less promising than infliximab; they consist of antiinflammatory cytokines, inhibitors of proinflammatory cytokines, hormones and growth factors: anti-IL 12-antibody, interferon-alpha, interferon-beta, G-CSF, GM-CSF, EGF, growth hormone, anti-interferon-gamma, anti-IL-18, anti-IL-2-%receptor% and anti-CD3 antibodies. The evaluation of other biological drugs has been suspended for severe side effects as happened for anti-CD40L antibody causing thromboembolism and anti-CD4 antibody causing ly.mphopenia. Other compounds as IL-10 and IL-11 have been proven to be ineffective even if an oral formulation of IL-11 is under evaluation. Among the MAP kinases inhibitors BIRB-796 and RDP58 showed to be ineffective while CNI-1493 is under evaluation. The effort in identifying specific patients features predicting therapy response and the possible combination of different biological therapies represent undoubtedly a very promising perspective. Aim of this article is to review the biological compounds and their efficacy in IBD. (c) 2006 Bentham Science Publishers Ltd.

2/7/51 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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13824982 EMBASE No: 2006206600
Ex vivo gene therapy approaches to cartilage repair
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Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 20 MAY 2006, 58/2 (259-284)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X06000184
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 223

Degeneration of articular cartilage is one of the great clinical challenges that still lack a convincing therapeutic solution. Traumatically induced lesions and final stages of osteoarthritis with substantial loss of cartilage tissue require the generation of new hyaline cartilage, because significant endogenous repair does not occur. Current joint-preserving surgical approaches, however, mostly lead to fibrous repair tissue that is rapidly degraded. In experimental studies, several differentiation factors have been shown to stimulate chondrogenesis, promoting the formation of functionally acceptable cartilage-like repair tissue. Cell-mediated transfer of the respective genes may ideally combine the supply of a chondrogenic cell population with the production of such factors directly at the site of the lesion. The treatment of earlier disease stages aims both at the protection of the remaining cartilage from further degradation and a stimulation of cartilage anabolism. Various studies proved the administration of anti-catabolic or anti-inflammatory cytokines into joints affected by cartilage destruction to be beneficial. However, the clinical utility of intraarticular protein application is limited by the short half-lives of such proteins in vivo. The transfer of cells over-expressing the respective genes may provide a more sustained delivery of the therapeutic molecules and thus be the more economic option. (c) 2006 Elsevier B.V. All rights reserved.

2/7/52 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

13823549 EMBASE No: 2006208664
Cytokine and anti-cytokine therapies for psoriasis and atopic dermatitis
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BioDrugs (BIODRUGS) (New Zealand) 2006, 20/2 (93-103)
CODEN: BIDRF ISSN: 1173-8804 eISSN: 1173-8804
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 86

Since the discovery of cytokines as key mediators in inflammation, targeting the cytokine network has represented a promising therapeutic approach. Psoriasis and atopic dermatitis, as T cell-mediated diseases with a strong cytokine component and a high unmet medical need, have moved into the focus of experimental therapies. Whereas pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha are overexpressed in both diseases, a type 1 cytokine pattern predominates in psoriasis and a type 2 cytokine pattern is of pathophysiological importance at least in the initial stages of atopic dermatitis. Strategies for intervention into the cytokine network have included antagonism of pro-inflammatory cytokines (e.g. TNFalpha, interleukin [IL]-1, IL-8, IL-12, IL-18, IL-23) with neutralizing antibodies and %soluble% %receptors%, application of recombinant cytokines (e.g. IL-4, IL-10, IL-11, interferon [IFN]-gamma) to shift the cytokine balance, and administration of small molecules to modulate cytokine expression or signaling. Results from the clinic have led to novel therapeutic options as well as a better understanding of the pathophysiology of inflammatory skin diseases. This review highlights the various therapeutic strategies, results from the clinic (that are in some cases preliminary), and insights that can be drawn from the more advanced clinical studies and the use of approved cytokine-directed therapies. (c) 2006 Adis Data Information BV. All rights reserved.

2/7/53 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

13508742 EMBASE No: 2006002275
Advances in therapeutic approaches to ulcerative colitis and Crohn's disease
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CODEN: CGRUA ISSN: 1522-8037
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 83

Advances (from 2004 to 2006) in the use of conventional agents include the molecular mechanisms of action, which have implications for monitoring (azathioprine and thioguanosine triphosphate) and chemoprevention (mesalamine and peroxisome proliferator activated receptor [PPAR]gamma). Advances in biotherapy include new data on monoclonal antibodies (infliximab in ulcerative colitis, adalimumab, certolizumab pegol, fontolizumab, selective anti-adhesion molecules, and others), antisense oligonucleoticles, the development of small molecules, and cell-gene therapy (including helminth ova, leukocytapheresis, stem cell transplantation, and probiotic intestinal mucosal delivery systems). However, management of inflammatory bowel disease is about more than drug therapy, dose, and timing. The goals remain induction of remission, limitation of side effects, modification of the pattern of disease, and avoidance of complications. With the cost and complexity of biotherapy, inflammatory bowel disease is emerging as a specific subspecialty. Copyright (c) 2005 by Current Science Inc.

2/7/54 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

12849116 EMBASE No: 2004445211
Immunobiologic therapies for myelodysplastic syndrome
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Best Practice and Research in Clinical Haematology (BEST PRACT. RES. CLIN. HAEMATOL.) (United Kingdom) 2004, 17/4 SPEC.ISS. (653-661)
CODEN: BPRCA ISSN: 1521-6926
PUBLISHER ITEM IDENTIFIER: S1521692604000908
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 40

Recent progress in understanding the pathobiology of the myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have led to the development of various immunologically oriented therapies for these diseases. The existence of elevated levels of tumor necrosis factor-alpha (TNF-alpha) in %bone% marrow during early stages of MDS, and the possibility that TNF-(is proportional to) suppresses normal hematopoiesis led to studies of attempts to block the activity of TNF-alpha. An anti-TNF monoclonal antibody and an antibody comprised of the %soluble% extracellular ligand-binding portion of the TNF %receptor% have both been evaluated recently in several small pilot studies. The recognition that marrow suppression in MDS may, in part, be a T-cell mediated autoimmune process has stimulated various trials of antithymocyte globulin and other similar agents. Gemtuzumab ozogamicin, an antibody against CD33 conjugated to the cytotoxic agent calicheamicin, is approved for use in AML and is currently being investigated as a potential therapeutic agent in MDS. Clinical trials were conducted as either monotherapy or in combination with cytokines such as IL-11 and chemotherapeutic agents including idarubicin, fludarabine, and/or cytarabine. Other antibodies are being developed as immunoconjugates with radioisotopes as part of conditioning regimens prior to %bone% marrow transplantation for AML or MDS. These include SUP131I-anti-CD45 antibody (BC8). SUP131 I anti-CD33 antibody (p67), SUP213Bi-M195 antibody, and

SUP188Re-labeled anti-CD66 antibody. The clearest example of successful immunotherapy for MDS (and AML) is the use of the graft-versus-tumor effect associated with allogeneic hematopoietic cell transplantation. Recently, nonmyeloablative transplants have been explored with encouraging results. Vaccines using overexposed self-antigens such as WT1 and PR1 are other attempts to induce a T-cell mediated response against MDS.

2/7/55 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

12683905 EMBASE No: 2004277663
Regulation of haematopoiesis by growth factors - Emerging insights and therapies
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Expert Opinion on Biological Therapy (EXPERT OPIN. BIOL. THER.) (United Kingdom) 2004, 4/6 (869-879)
CODEN: EOBTA ISSN: 1471-2598
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 91

Haematopoiesis is regulated by a wide variety of glycoprotein hormones, including stem cell factor, granulocyte-macrophage colony-stimulating factor, thrombopoietin and IL-3. These haematopoietic growth factors (HGFs) share a number of properties, including redundancy, pleiotropy, autocrine and paracrine effects, receptor subunit oligomerisation and similar signal transduction mechanisms, yet each one has a unique spectrum of haematopoietic activity. Ongoing studies with knockout mice have discovered previously unrecognised physiological roles for HGFs, linking haematopoiesis to innate immunity, pulmonary physiology and %bone% metabolism. The regulation of stem cells by HGFs within niches of the %bone% marrow microenvironment is now well recognised and similar mechanisms appear to exist in the regulation of other stem cell compartments. Alternative signalling strategies, other than tyrosine kinase activation and phosphotyrosine cascades, may account for some of the more subtle differences between HGFs. Accumulating evidence suggests that some, but not all, HGF receptors can transduce a genuine lineage-determining signal at certain points in haematopoiesis. Further studies, primarily at the receptor level, are needed to determine the mechanisms of instructive signalling, which may include phosphoserine cascades. Novel haematopoietic regulators, as well as the development of biological therapies, including growth factor antagonists and %peptide% mimetics, are also discussed.

2/7/56 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

12654010 EMBASE No: 2004246489
Maintenance of remission in Crohn's disease: Current and emerging therapeutic options
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Drugs (DRUGS) (New Zealand) 2004, 64/10 (1069-1089)
CODEN: DRUGA ISSN: 0012-6667
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 161

Crohn's disease is a chronic inflammatory bowel disorder with a relapsing and remitting course. Once remission is achieved, the main aim of the management of Crohn's disease is maintenance of that remission. Significant advances have been made into understanding the aetiology and pathogenesis of inflammatory bowel disease. With these advances in understanding come increasing numbers of new agents and therapies, aimed both at active disease and the subsequent maintenance of remission in Crohn's disease. Current therapeutic strategies in maintaining remission in Crohn's disease include 5-aminosalicylates (e.g. sulfasalazine, mesalazine), thiopurines (e.g. azathioprine, 6-mercaptopurine [mercaptopurine]), methotrexate and infliximab. The 5-aminosalicylates appear to have efficacy limited to either surgically induced remission and/or limited small bowel Crohn's disease. The immunomodulators now have an established role in Crohn's maintenance. Azathioprine and 6-mercaptopurine are effective in chronic active disease and corticosteroid-dependant Crohn's disease. Methotrexate has similar indications, although it appears to be an alternative in patients who are intolerant of, or resistant to, the thiopurines. The most recent breakthrough has been in the field of biological therapy for maintenance of remission in Crohn's disease. Treatment of patients with the anti-tumour necrosis factor (TNF)-alpha antibody infliximab has been shown already to be effective in inducing remission. Recent studies have now confirmed a role for infliximab in delaying relapse and maintaining remission in patients responsive to infliximab induction therapy. However, results with %soluble% TNFalpha %receptors% have been disappointing. A number of other biological and nonbiological agents have shown potential, though trials of the 'newer' biological agents have thus far been disappointing, in the maintenance of remission in Crohn's disease. The evidence for theses agents is currently limited, in many cases to treating active disease; however, these data are discussed in this article in order to provide an overview of future potential therapies. The aim of this review is to provide clinicians with an insight into current and emerging therapeutic agents for the maintenance of remission of Crohn's disease.

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DIALOG(R)File 73:EMBASE

12388008 EMBASE No: 2003491072
%Soluble% Mannose 6-Phosphate/Insulin-Like Growth Factor II (IGF-II) %Receptor% Inhibits Interleukin-6-Type Cytokine-Dependent Proliferation by Neutralization of IGF-II
Duplomb L.; Chaigne-Delalande B.; Vusio P.; Raher S.; Jacques Y.; Godard A.; Blanchard F.
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Endocrinology (ENDOCRINOLOGY) (United States) 2003, 144/12 (5381-5389)
CODEN: ENDOA ISSN: 0013-7227
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 48

The calcium-independent mannose 6-phosphate %receptor% (CIMPR) is a %receptor% for multiple ligands, including leukemia inhibitory factor (LIF), an IL-6 type cytokine, and IGF-II. CIMPR targets newly synthesized ligands to lysosomes and induces internalization/degradation of secreted ligands. A natural %soluble% form of CIMPR (sCIMPR) neutralizes IGF-II mitogenic potency on hepatocytes and fibroblasts. Herein we show that sCIMPR also inhibits LIF-driven proliferation of myeloid and lymphoid cell lines. Similar inhibition was observed with IL-6 and IL-11, two other IL-6-type cytokines that do not interact with CIMPR. Neutralizing anti-IGF-II antibodies inhibited IL-6-, IL-11-, and LIF-driven cell proliferation to the same extent as sCIMPR, suggesting that neutralization of serum IGF-II by sCIMPR plays a major role in IL-6-type cytokine-dependent cell proliferation. Confirming this idea, ERK1/2 and AKT/protein kinase B, the kinases necessary for cell proliferation and survival, were activated by IGF-II alone or by the association of IL-6-type cytokines and IGF-II. IL-6-type cytokines alone (up to 10 ng/ml) did not activate ERK1/2 or AKT, but did activate STAT3 (signal transducer and activator of transcription 3), a transcription factor necessary for the GSUB1 to S phase cell cycle transition. Activation of ERK1/2 and AKT by IGF-II thus appears essential to sustain cellular expansion driven by

IL-6-type cytokines.

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DIALOG(R)File 73:EMBASE
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12237419 EMBASE No: 2003342817
Hematopoietic stimulation by a dipeptidyl peptidase inhibitor reveals a novel regulatory mechanism and therapeutic treatment for blood cell deficiencies
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Blood (BLOOD) (United States) 01 SEP 2003, 102/5 (1641-1648)
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In hematopoiesis, cytokine levels modulate blood cell replacement, self-renewal of stem cells, and responses to disease. Feedback pathways regulating cytokine levels and targets for therapeutic intervention remain to be determined. Amino boronic dipeptides are orally bioavailable inhibitors of dipeptidyl peptidases. Here we show that the high-affinity inhibitor Val-boro-Pro (PT-100) can stimulate the growth of hematopoietic progenitor cells in vivo and can accelerate neutrophil and erythrocyte regeneration in mouse models of neutropenia and acute anemia. Hematopoietic stimulation by PT-100 correlated with increased cytokine levels in vivo. In vitro, PT-100 promoted the growth of primitive hematopoietic progenitor cells by increasing granulocyte - colony-stimulating factor (G-CSF), interleukin-6 (IL-6), and IL-11 production by %bone% marrow stromal cells. Two molecular targets of PT-100 are expressed by stromal cells - CD26/DPP-IV and the closely related fibroblast activation protein (FAP). Because PT-100 was active in the absence of CD26, FAP appears to be the hematopoietic target for PT-100. Interaction of PT-100 with the catalytic site seems to be required because amino-terminal acetylation of PT-100 abrogated enzyme inhibition and hematopoietic stimulation. PT-100 is a therapeutic candidate for the treatment of neutropenia and anemia. The data support increasing evidence that dipeptidyl peptidases can regulate complex biologic systems by the proteolysis of signaling %peptides%. (c) 2003 by The American Society of Hematology.

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DIALOG(R)File 73:EMBASE
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12078880 EMBASE No: 2003185192
A review of the cytokine network in multiple myeloma: Diagnostic, prognostic, and therapeutic implications
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Cancer (CANCER) (United States) 15 MAY 2003, 97/10 (2440-2452)
CODEN: CANCA ISSN: 0008-543X
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 41

Because many studies have focused on growth factors in multiple myeloma, the study of the cytokine network appears to be useful for this purpose. Interleukin-6 (IL-6) and IL-2 with their %soluble% %receptors% (IL-3, IL-4, IL-10, and IL-11) have been examined. Plasma cells may produce IL-6 by an autocrine mechanism whereas a paracrine mechanism is believed to be involved in the production of IL-6 by %bone% marrow stromal cells through an interaction between adhesion molecules present on myeloma plasma cells and their respective %receptors% that are present on %bone% marrow stromal cells. In addition, control over production of IL-6 may be exerted by other ILs such as IL-1beta and IL-10. Among target cells, the growth of normal and myeloma plasma cells is supported by IL-6, which also induces the differentiation of myeloma plasmablastic cells into mature plasma cells. This last action also is shared by IL-3, IL-4, and, most likely, IL-8. Evaluation of the serum level of IL-6, C reactive protein, %soluble% IL-6 %receptor% (sIL-6R), and %soluble% IL-2 %receptor% (sIL-2R), together with the activity exerted by IL-3 and IL-4 on some cellular subsets, may constitute an additional element in the differential diagnosis of borderline cases. However, the concomitant evaluation of all immunologic parameters could be more useful than the value of a single IL. Serum levels of IL-6, sIL-6R, sIL-2R, and the expression of membrane-bound IL-2 %receptors%, both on %bone% marrow plasma cells and on peripheral blood mononuclear cells, are correlated with disease activity and disease stage. In addition, IL-6 and sIL-6R serum levels are believed to be correlated with the duration of disease-free survival because a high serum level at the time of diagnosis is believed to be correlated with a short duration of survival. However, some laboratory parameters may express the same prognostic value as high betaSUB2 microglobulin and lactate dehydrogenase (LDH) serum levels together with a high plasma cell labeling index are correlated with disease activity. Furthermore, if the evaluation is performed at the time of diagnosis, high values of these parameters are correlated with a short disease-free survival. A correlation between laboratory parameters and the serum level of several cytokines was demonstrated. Hence, the real advantage of the prognostic evaluation of cytokines is reserved for patients who do not exhibit uniform results with regard to betaSUB2 microglobulin and LDH serum levels, or, better, for borderline cases. With regard to the differential diagnosis, all immunologic parameters should be evaluated concomitantly rather than separately to confer a real prognostic value to results. Furthermore, a particular relation was found between a high sIL-6R serum level and a poor response to chemotherapy, therefore suggesting the possibility of identifying in advance a subset of patients with a high risk of treatment failure, as has already been demonstrated in other hematologic malignancies. Finally, the majority of studies indicate that interferons are used mainly in the immunotherapy for multiple myeloma, whereas many clinical trials should still be required for the evaluation of the effectiveness of anti-I-L6 antibodies or antiidiotypic vaccines in reference to the eligible patients for these particular therapies. (c) 2003 American Cancer Society.

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The mode of action of cytokine inhibitors
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

Tumor necrosis factor-alpha (TNF-alpha) and interleukin 1 (IL-1) are important mediators of inflammation and tissue damage in animal models of inflammatory arthritis and in patients with active rheumatoid arthritis (RA). Several inhibitors of these cytokines are now available for RA treatment, each having a different mode of action. Etanercept is a recombinant fusion protein of the %soluble% type II TNF %receptor% on a human IgGSUB1 backbone, whereas infliximab is a chimeric anti-TNF-alpha monoclonal antibody containing a murine TNF-alpha binding region and human IgGSUB1 backbone. Both agents potently and selectively bind TNF-alpha in the cellular microenvironment, thereby preventing TNF-alpha from interacting with membrane-bound TNF %receptors% on target cells. In

comparison, anakinra is a recombinant human IL-1 %receptor% antagonist (IL-1Ra) that binds avidly to type 1 IL-1 %receptors% but does not stimulate any intracellular responses. Studies of these agents in animal models of inflammatory arthritis suggest that TNF-alpha plays a more important role in promoting inflammation, whereas IL-1 is more important in causing cartilage and %bone% destruction. However, these differential actions have not been borne out in clinical trials, where TNF-alpha blockers and anakinra similarly reduce clinical signs and symptoms of RA as well as slow radiographic evidence of disease progression.

2/7/61 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

11463326 EMBASE No: 2002034772
Interleukin-6 and the network of several cytokines in multiple myeloma: An overview of clinical and experimental data
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Cytokine (CYTOKINE) (United Kingdom) 07 NOV 2001, 16/3 (79-86)
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 75

Study of the network of cytokines has helped identify cell growth factors in multiple myeloma. Plasma cells themselves may produce autocrine interleukin 6 (IL-6) while IL-6 production by %bone% marrow stromal cells may operate a paracrine mechanism. Involvement of IL-6 in multiple myeloma is indicated by its ability to induce the differentiation of myeloma plasmablasts into mature malignant plasma cells. Differential diagnosis between multiple myeloma and monoclonal gammopathies of undetermined significance (MGUS) is generally based on clinical and laboratory parameters. Nevertheless, evaluation of the serum level of IL-6, C reactive protein, %soluble% IL-6 %receptor%, %soluble% IL-2 %receptor% together with the activity exerted by IL-3 and IL-4 on some cellular subsets constitutes an additional element in the differential diagnosis of border-line cases. Serum levels of IL-6, %soluble% IL-6 %receptor% (sIL-6R), %soluble% interleukin-2 %receptor% (sIL-2R) and the expression of membrane-bound IL-2 %receptors%, both on %bone% marrow plasma cells and on peripheral blood mononuclear cells are correlated with disease activity and disease stage. In addition, IL-6 and sIL-6R serum levels correlate with the duration of survival, as high values at the time of diagnosis correlate with short duration of survival. (c) 2001 Academic Press.

2/7/62 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE

11262862 EMBASE No: 2001277758
Multipotent hematopoietic progenitor cells immortalized by Lhx2 self-renew by a cell nonautonomous mechanism
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Experimental Hematology (EXP. HEMATOL.) (United States) 2001, 29/8 (1019-1028)
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DOCUMENT TYPE: Journal ; Article
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NUMBER OF REFERENCES: 51

Objective: Direct molecular and cellular studies of hematopoietic stem cells (HSCs) are hampered by the low levels of HSCs in hematopoietic tissues. To address these issues, we generated immortalized multipotent hematopoietic precursor cell (HPC) lines by expressing the LIM-homeobox gene Lhx2 (previously LH2) in hematopoietic progenitors derived from embryonic stem cells differentiated in vitro. Materials and Methods: To validate further the relevance of the HPC lines as a model for normal HSCs, we analyzed in detail the growth requirements of HPC lines in vitro. Results: Lhx2 immortalized the HPC lines by a putatively novel and cell nonautonomous mechanism. Self-renewal of the HPC lines is dependent on functional Lhx2 expression. Most early-acting hematopoiesis-related growth factors show synergistic effects on the HPC lines, whereas late-acting factors do not induce differentiation by themselves. Transforming growth factor-betaSUB1 is a potent inhibitor of proliferation of the HPC lines. HPC lines form cobblestone areas with high efficiency when seeded onto stromal cell lines, and the cobblestone area-forming cell can be maintained in these cultures for several months. Conclusions: Our data show that, in many respects, HPC lines are similar to normal hematopoietic progenitor/stem cells on the cellular level, in contrast to most previously described multipotent hematopoietic cell lines. The cell nonautonomous mechanism for immortalization of the HPC lines suggests that Lhx2 regulates, directly or indirectly, %soluble% mediators involved in self-renewal of the HPC lines. Copyright (c) 2001 International Society for Experimental Hematology.

2/7/63 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

11046308 EMBASE No: 2000390133
High levels of %soluble% syndecan-1 in myeloma-derived %bone% marrow: Modulation of hepatocyte growth factor activity
Seidel C.; Borset M.; Hjertner O.; Cao D.; Abildgaard N.; Hjorth-Hansen H.; Sanderson R.D.; Waage A.; Sundan A.
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DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 52

Syndecan-1 is a heparan sulfate proteoglycan expressed on the surface of, and actively shed by, myeloma cells. Hepatocyte growth factor (HGF) is a cytokine produced by myeloma cells. Previous studies have demonstrated elevated levels of syndecan-1 and HGF in the serum of patients with myeloma, both of negative prognostic value for the disease. Here we show that the median concentrations of syndecan-1 (900 ng/mL) and HGF (6 ng/mL) in the marrow compartment of patients with myeloma are highly elevated compared with healthy controls and controls with other diseases. We show that syndecan-1 isolated from the marrow of patients with myeloma seems to exist in an intact form, with glucosaminoglycan chains. Because HGF is a heparan-sulfate binding cytokine, we examined whether it interacted with %soluble% syndecan-1. In supernatants from myeloma cells in culture as well as in pleural effusions from patients with myeloma, HGF existed in a complex with %soluble% syndecan-1. Washing myeloma cells with purified %soluble% syndecan-1 could effectively displace HGF from the cell surface, suggesting that %soluble% syndecan-1 can act as a carrier for HGF in vivo. Finally, using a sensitive HGF bioassay (%interleukin%-%11% production from the osteosarcoma cell line Saos-2) and intact syndecan-1 isolated from the U-266 myeloma cell line, we found that the presence of high concentrations of syndecan-1 (more than 3 mug/mL) inhibited the HGF effect, whereas lower concentrations potentiated it. HGF is only one of several heparin-binding cytokines associated with myeloma. These data indicate that %soluble% syndecan-1 may participate in the pathology of myeloma by modulating cytokine activity within the %bone% marrow. (C) 2000 by The American Society of Hematology.

2/7/64 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE

10852500 EMBASE No: 2000334138
Protein expression and functional difference of membrane-bound and %soluble% %receptor% activator of NF-kappaB ligand: Modulation of the expression by osteotropic factors and cytokines
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Biochemical and Biophysical Research Communications (BIOCHEM. BIOPHYS. RES. COMMUN.) (United States) 07 SEP 2000, 275/3 (768-775)
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

A variety of humoral factors modulate the osteoclastogenesis. %Receptor% activator of NF-kappaB ligand (RANKL) expressed on osteoblast/stromal lineage cells plays a pivotal role to transduce an essential differentiation signal to osteoclast lineage cells through binding to its %receptor%, RANK, expressed on the latter cell population; however, the difficulty to detect RANKL protein expression hampers us in investigating the regulation of RANKL expression by humoral facotrs. To determine protein expression of RANKL, we have established a new method, named as a ligand-%receptor% precipitation (LRP) Western blot analysis, which can specifically concentrate the target protein by the use of specific binding characteristic between RANKL and RANK/osteoprotegrin (OPG). RANKL protein expression in the postnuclear supernatant was not detected by common Western blotting, but LRP Western blot analysis clearly showed that RANKL is produced as a membrane-bound protein on murine osteoblasts/stromal cells, and cleaved into a %soluble% form by metalloprotease. Cytokines stimulating the osteoclastogenesis, such as IL-1beta, IL-6, IL-11, IL-17, and TNF-alpha, increased the expression of RANKL with decrease of OPG expression in osteoblasts/stromal cells. In contrast, cytokines inhibiting the osteoclastogenesis, such as IL-13, INF-gamma, and TGF-beta1 suppressed the expression of RANKL and/or augmented OPG expression. Functional difference between membrane-bound and %soluble% RANKL was demonstrated, which showed that membrane-bound RANKL works more efficiently than %soluble% RANKL in the osteoclastogenesis developed from murine %bone% marrow cell culture. The present study indicates the usefulness of LRP Western blot analysis, which shows that the modulation of osteoclastogenesis by humoral factors is achieved, in part, by regulation of the expression of RANKL and OPG in osteoblast/stromal lineage cells. (C) 2000 Academic Press.

2/7/65 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

07406289 EMBASE No: 1998315001
Mode of action of interleukin-6 on mature osteoclasts. Novel interactions with extracellular Casup 2sup + sensing in the regulation of osteoclastic %bone% resorption
Adebanjo O.A.; Moonga B.S.; Yamate T.; Sun L.; Minkin C.; Abe E.; Zaidi M.
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Journal of Cell Biology (J. CELL BIOL.) (United States) 07 SEP 1998, 142/5 (1347-1356)
CODEN: JCLBA ISSN: 0021-9525
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

We describe a physiologically significant mechanism through which interleukin-6 (IL-6) and a rising ambient Casup 2sup + interact to regulate osteoclastic %bone% resorption. VOXEL-based confocal microscopy of nonpermeabilized osteoclasts incubated with anti-IL-6 %receptor% antibodies revealed intense, strictly peripheral plasma membrane fluorescence. IL-6 %receptor% expression in single osteoclasts was confirmed by in situ reverse transcriptase PCR histochemistry. IL-6 (5 ng/l to 10 mug/l), but not IL-11 (10 and 100 mug/l), reversed the inhibition of osteoclastic %bone% resorption induced by high extracellular Casup 2sup + (15 mM). The IL-6 effect was abrogated by excess %soluble% IL-6 %receptor% (500 mug/l). Additionally, IL-6 (5 pg/l to 10 mug/l) inhibited cytosolic Casup 2sup + signals triggered by high Casup 2sup + or Nisup 2sup +. In separate experiments, osteoclasts incubated in 10 mM Casup 2sup + or on %bone% released more IL-6 than those in 1.25 mM Casup 2sup +. Furthermore, IL-6 mRNA histostaining was more intense in osteoclasts in 10 or 20 mM Casup 2sup + than cells in 1.25 mM Casup 2sup +. Similarly, IL-6 %receptor% mRNA histostaining was increased in osteoclasts incubated in 5 or 10 mM Casup 2sup +. Thus, while high Casup 2sup + enhances IL-6 secretion, the released IL-6 attenuates Casup 2sup + sensing and reverses inhibition of resorption by Casup 2sup +. Such an autocrine-paracrine loop may sustain osteoclastic activity in the face of an inhibitory Casup 2sup + level generated locally during resorption.

2/7/66 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

07142170 EMBASE No: 1998019415
Growth factors and hematopoietic stem cells
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Hematology/Oncology Clinics of North America (HEMATOL. ONCOL. CLIN. NORTH AM.) (United States) 1997, 11/6 (1173-1184)
CODEN: HCNAE ISSN: 0889-8588
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 142

The hematopoietic system is mediated in part by cell-to-cell interactions and %soluble% mediators or growth factors (cytokines). A large number of cytokines directly and potently control hematopoietic stem and precursor cell proliferation and differentiation. This review focuses on the recent studies devoted to the role of cytokines in the ex vivo expansion and differentiation of hematopoietic stem and precursor cells.

2/7/67 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE

06699149 EMBASE No: 1996364090
%Soluble% thrombopoietin %receptor% (Mpl) and granulocyte colony-stimulating factor %receptor% directly stimulate proliferation of primitive hematopoietic progenitors of mice in synergy with steel factor or the ligand for Flt3/Flk2
Ku H.; Hirayama F.; Kato T.; Miyazaki H.; Aritomi M.; Ota Y.; D'Andrea A.D.; Lyman S.D.; Ogawa M.
VA Medical Center, 109 Bee St,Charleston, SC 29401-5799 United States
Blood (BLOOD) (United States) 1996, 88/11 (4124-4131)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In an effort to establish the specificity of the thrombopoietin (TPO) effects on murine multipotential progenitors, we tested the effects of %soluble% TPO %receptor% (sTPOR; sMpl) on multilineage colony formation that was supported by a combination of TPO and steel factor (SF). Surprisingly, sTPOR did not suppress colony formation from primitive

progenitors. This led to the discovery that sTPOR synergizes with SF or Flt3/Flk2 ligand (FL) to support the formation of various types of hematopoietic colonies including multilineage colonies. The colonies supported by the combination of sTPOR and SF were capable of expressing both myeloid and B-lymphoid potentials. Studies using micromanipulation and serum-free culture showed that the effects of sTPOR and SF on the primitive progenitors are direct, not mediated by contaminating stromal cells, and not dependent on factors present in the serum. TPOR belongs to the cytokine %receptor% group that includes granulocyte colony-stimulating factor %receptor% (G-CSFR) and erythropoietin %receptor% (EPOR). Therefore, we tested the effects of sG-CSFR and sEPOR on primitive progenitors. sG-CSFR, but not sEPOR, was able to synergize with SF or FL in supporting the proliferation of primitive progenitors. The direct effects of the %soluble% %receptors% appear to be mediated through interactions with their respective membrane-bound %receptors% expressed on the primitive hematopoietic progenitors.

2/7/68 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE
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06620927 EMBASE No: 1996285708
Thrombopoietin stimulates colony-forming unit-megakaryocyte proliferation and megakaryocyte maturation independently of cytokines that signal through the gp130 %receptor% subunit
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Blood (BLOOD) (United States) 1996, 88/6 (2026-2032)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Thrombopoietin (Tpo), the ligand for the c-Mpl %receptor%, is a major regulator of megakaryopoiesis. Treatment of mice with Tpo raises the platelet count fourfold within a few days. Conversely, c-mpl knock-out mice have platelet counts that are 15% that of normal. The subunit structure of the c- Mpl %receptor% is not fully understood. Some cytokines that stimulate megakaryopoiesis (IL-6, IL-11, leukemia inhibitory factor, and oncostatin M) bind to %receptors% that use gp130 as a signal transduction subunit. For these reasons, we determined whether gp130 function was required for Tpo-induced signal transduction. Murine marrow cells were cultured in semi-solid media in the presence of Tpo or IL-3, with or without a neutralizing anti-gp130 monoclonal antibody (RX187) or a %soluble% form of c-Mpl %receptor% (%soluble% Mpl) that blocks Tpo bioactivity, and the numbers of colony-forming unit- megakaryocyte (CFU-Meg) colonies were counted on day 5. Murine marrow cells were also cultured in suspension under serum-free conditions for 5 days, and megakaryocyte DNA content was measured by flow cytometry, as an index of nuclear maturation. The addition of RX187 did not block Tpo-induced CFU-Meg colony growth nor CFU-Meg nuclear maturation in suspension culture. However, IL-3-induced CFU-Meg colony growth and megakaryocyte nuclear maturation decreased in the presence of RX187. %Soluble% Mpl completely ablated Tpo- induced CFU-Meg growth, and partially blocked IL-3-stimulated CFU-Meg growth. Thus the effects of Tpo on megakaryopoiesis in vitro do not depend on cytokines that signal through gp130. Furthermore, it is unlikely that gp130 serves as a beta chain for the c-Mpl %receptor%, as Tpo signalling is unimpaired in the presence of RX187. In contrast, the effects of IL-3 on CFU- Meg growth are mediated in part through Tpo and through gp130-signalling cytokines.

2/7/69 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE
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06110739 EMBASE No: 1995141430
Contact- and growth factor-dependent survival in a canine marrow-derived stromal cell line
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Blood (BLOOD) (United States) 1995, 85/9 (2414-2421)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cell-cell interactions and the presence of growth factors such as stem cell factor (SCF; or c-kit ligand) or interleukin-6 (IL-6) are involved in the proliferation and differentiation of the canine marrow-derived stromal cell line DO64. In the presence of SCF, stromal cells are induced to differentiate, but not to proliferate. In contrast, in the presence of IL-6, stromal cells are induced to proliferate rather than to differentiate in culture. Both SCF and IL-6 are produced by the stromal cells themselves and, thus, act as autocrine factors. In addition, DO64 cells also interact physically with each other in culture when grown under optimal culture conditions (70% to 90% cell confluence and in the presence of serum), thereby supporting proliferation and maintaining viability. Under conditions of lower cell density or low serum or growth factor concentrations in culture, DO64 cells tend to aggregate and form clusters. This increase in local cell concentration is associated with preservation of viability, presumably because of the accumulation of autocrine factors. If no signal, neither intercellular nor %soluble%, is provided, and DO64 cells are not able to reach a critical cell density or to produce sufficient factors in an autocrine fashion, the cells cease to proliferate and eventually die.

2/7/70 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.
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0411662 DBR Accession No.: 2006-25158 PATENT
New isolated umbilicus-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, useful for treating %bone%, pancreatic, kidney, or neural disease or injury - mammal cell culture medium and differentiation for use in disease therapy and tissue engineering
AUTHOR: HARRIS I R; MESSINA D J; KIHM A J; SEYDA A; COLTER D C
PATENT ASSIGNEE: ETHICON INC 2006
PATENT NUMBER: US 20060223177 PATENT DATE: 20061005 WPI ACCESSION NO.: 2006-688933 (200671)
PRIORITY APPLIC. NO.: US 315897 APPLIC. DATE: 20051222
NATIONAL APPLIC. NO.: US 315897 APPLIC. DATE: 20051222
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated umbilicus-derived cell comprising a cell derived from mammalian umbilical cord tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a cell culture comprising the isolated cell, which is free of maternal cells; (2) a therapeutic cell culture comprising the isolated cell; (3) a method of deriving, from umbilical tissue, an isolated cell, the cell capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes; (4) an isolated human umbilicus-derived cell derived by the method above; (5) a therapeutic culture of human umbilicus-derived cells derived by the method above, where the culture is free of maternal cells; (6) a conditioned culture medium generated by the growth of the culture; (7) a mammalian cell culture comprising the conditioned medium and a mammalian cell in need of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1; (8) a three dimensional matrix comprising the umbilicus-derived cell;(9) an implantable tissue structure comprising the matrix; (10) an implantable device comprising the therapeutic cell; (11) an implantable human tissue matrix comprising the cell; (12) a human tissue comprising the cell; (13) a cell lysate derived from the cell; (14) a %soluble% cell fraction derived from the cell; (15) a membrane-enriched cell fraction derived from the cell; (16) an extracellular membrane fraction derived

from the cell; (17) an injectable therapeutic cell comprising an isolated human umbilicus-derived cell; (18) a method for the preparation of therapeutic cells or cultures; (19) a serum-free medium for the expansion of postpartum-derived cells, where the medium has one or more growth factors added; (20) a therapeutic culture comprising postpartum-derived cells expanded in serum-free medium; and (21) a cell culture bank comprising the cells. BIOTECHNOLOGY - Preferred Cell: The cell can expand in the presence of oxygen from 5-20%. It also requires L-valine for growth. The isolated cell can double sufficiently to generate yields of greater than 1014 to 1017 cells in less than 80 days in culture when seeded at 103 to 5x103 cells/cm2. It can also undergo at least 40 doublings in culture. Preferably, the cell is isolated from human umbilicus. It is isolated in the presence of one or more enzyme activities comprising metalloproteases, neutral proteases, or mucolytic enzymes. The enzyme activities include at least one collagenase, and one or more of the protease activities, dispase, and thermolysin. The enzyme activities are also collagenase from Clostridium histolyticum and dispase. The enzyme activities further include hyaluronidase. The isolated cell attaches and expands on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating with gelatin, laminin, collagen, polyornithine, polylysine, vitronectin, or fibronectin. It also expands in the presence of 2-15% added serum, in the presence or absence of beta-mercaptoethanol, and in the presence or absence of added growth factors including EGF, FGF, PDGF, VEGF, IGF or LIF. The isolated cell maintains a normal karyotype as it is passaged. It is characterized in its production or lack of production of one or more cell surface markers comprising CD10, CD13, CD31, CD44, CD45, CD73, CD90, CD117, CD141, PDGFr-alpha, HLA-A, B, C, or HL-Dr, DP, DQ. The cell produces one or more of, or each of, CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, or HLA-A, B, C. It does not produce one or more of, or any of, CD31, CD34, CD45, CD117, CD141, or HLA-DR, DP, DQ, as detected by flow cytometry. Preferably, the isolated CD45-umbilicus-derived cell had a cell surface marker profile, where the cell produces one or more of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, or HLA-A, B, C, and does not express one or more of CD31, CD34, CD117, CD141, or HLA-DR, DP, DQ, as detected by flow cytometry. The cell surface marker expression profile remains substantially unchanged with passage, culture vessel surface coating, or isolation procedure. The isolated cell expresses a gene for one or more of, or for each of, interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; or tumor necrosis factor, alpha-induced protein 3. The expression is increased relative to that of a human cell, which is a fibroblast, a mesenchymal stem cell, an ileac crest %bone% marrow cell, or placenta-derived cell. The isolated cell, which is relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, has reduced expression of one or more genes selected from short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams Beuren syndrome); Homo sapiens mRNA; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, antiproliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor%-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, betalike 1 (with EGF-like repeat domains); H. sapiens mRNA full-length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FL J14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19 kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36 kDa. Alternatively, the isolated human umbilicus-derived cell, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, has reduced expression of genes for each of short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams Beuren syndrome); H. sapiens mRNA; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, antiproliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, betalike 1 (with EGF-like repeat domains); H. sapiens mRNA full-length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FL J14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19 kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36 kDa, and which expresses a gene for each of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3, where the expression is increased relative to that of a human cell which is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell. The isolated cell is capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes. It produces one or both of vimentin and alpha smooth muscle actin. The production of vimentin and alpha smooth muscle actin is retained over passaging under growth conditions. Alternatively, the isolated human umbilicus-derived cell capable of self-renewal and expansion in culture has the potential to differentiate into cells of other phenotypes, where the cell does not substantially stimulate naive CD4+ T cells, and expresses PD-L2, but not HLA-G, CD178, HLA-DR, HLA-DP, HLA-DQ, CD80, CD86, or B7-H2. The cell secretes one or more cellular factors, where the factors are MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1. The cell also secretes each of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, and TIMP1. The cell does not secrete one or more of the cellular factors SDF-1alpha, TGF-beta2, ANG2, PDGFbb, or VEGF, as detected by ELISA. Alternatively, the isolated human umbilicus-derived

cell secretes one or more of the factors MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1, and does not secrete one or more of the factors SDF-1alpha, TGF-beta2, ANG2, PDGFbb, or VEGF, as detected by ELISA. The injectable cell is treated to inactivate tissue factor. It is treated with an anti-tissue factor antibody. Alternatively, an isolated postpartum-derived cell comprises an L-valine-requiring cell derived from human postpartum tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into a cell of cardiomyocyte phenotypes; the cell capable of growth in an atmosphere containing oxygen from 5-20%; where the cell comprises at least one, or each of the following characteristics: (a) potential for at least 40 doublings in culture; (b) attachment and expansion on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; (c) production of at least one of tissue factor, vimentin, and alpha-smooth muscle actin; (d) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and HLA-A, B, C; (e) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CDII7, CD141, CD178, B7-H2, HLAG, and HLA-DR, DP, DQ, as detected by flow cytometry; (f) expression of at least one of interleukin 8, reticulon 1, chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha), chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2), chemokine (C-X-C motif) ligand 3, and tumor necrosis factor, alpha-induced protein 3; (g) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams Beuren syndrome); H. sapiens mRNA; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, antiproliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor%-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, betalike 1 (with EGF-like repeat domains); H. sapiens mRNA full-length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FL J14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19 kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36 kDa; (h) secretion of at least one of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIP1a, RANTES, and TIMP1; or (i) lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MIP1beta, 1309, MDC, and VEGF, as detected by ELISA. Alternatively, the isolated postpartum-derived cell comprises a signature gene profile, where mRNA from genes for reticulon, oxidized LDL %receptor%, and IL-8 are present independent of whether the cells are grown in medium containing serum or medium free of serum. It further comprises the ability to alter its expression of cell surface markers when grown in medium containing serum relative to that in serum free medium. The markers for PDGF-%receptor% alpha and HLAABC are altered. Preferred Cell Culture: The therapeutic cell culture does not substantially stimulate allogeneic PBMCs. It lacks detectable amounts of HLA-DR, HLA-DP, HLA-DQ, CD80, CD86, and B7-H2, as determined by flow cytometry. It further lacks detectable amounts of HLA-G and CD178, as determined by flow cytometry. The therapeutic cell culture produces detectable amounts of PD-L2, as determined by flow cytometry. It does not substantially stimulate a lymphocyte-mediated response in vitro, as compared to allogeneic controls in a mixed lymphocyte reaction. The therapeutic cell culture further comprises one or more of a pharmaceutical carrier, another cell culture, an anti-apoptotic compound, an anti-thrombogenic compound, an anti-inflammatory compound, an immunosuppressive compound, an immunomodulatory compound, an angiogenic factor, and a neurotrophic factor. The culture further comprises the umbilicus-derived cells and another mammalian cell of any phenotype. It also comprises a human cell line in addition to the umbilicus-derived cell. The therapeutic culture also comprises cells having a signature gene profile, where mRNA from genes for reticulon, oxidized LDL %receptor%, and IL-8 are present independent of whether the cells are grown in medium containing serum or medium free of serum. Preferred Method: Deriving, from umbilical tissue, an isolated cell, the cell capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes, comprises: (A) obtaining umbilical tissue; (B) removing substantially all of blood to yield a substantially blood-free umbilical tissue; (C) dissociating the tissue by mechanical or enzymatic treatment, or both; (D) resuspending the tissue in a culture medium; and (E) providing growth conditions, which allow for the growth of an umbilicus-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes. The method further comprises selecting adherent cells after 10-100 hours in culture. The umbilicus tissue is from a human. It is obtained after normal or surgically assisted childbirth from a full-term or pre-term pregnancy. The dissociation step comprises the use of one or more enzyme activities selected from metalloprotease, hyaluronidase, and neutral protease. Dissociating comprises incubating at 37degreesC. Incubating is for one or more hours, preferably 2 hours. The removing step comprises removal of free or clotted blood by one or more of washing, suctioning, blotting, centrifugal separation, or enzymatic removal. Dissociating step is accomplished aseptically. The dissociation step comprises one or more of mincing, blending, homogenizing, or grinding. Preparing therapeutic cells or cultures comprises: (A) isolating cells; (B) initially expanding the cells to a useful number in a serum-containing medium, which supports cell expansion but in which the cells produce a quantity of the cell surface marker HLA-ABC; (C) transferring the cells to a medium in which the cells produce a decreased amount of the cell surface marker HLA-ABC; and (D) passaging the cells in the medium in which the cells produce a decreased amount of the HLA-ABC, thus preparing a therapeutic cell or culture. The medium in which the cells produce a decreased amount of the cell surface marker HLA-ABC is a serum-free medium. The method is for the production of therapeutic cells or cultures for implantation or grafting. Preferred Matrix: The matrix comprises a biocompatible or bioabsorbable polymer. It comprises PGA/PLA copolymer, PCL/PGA copolymer, or self-assembling %peptides%. Preferred Serum-Free Medium: The growth factors added are bFGF, EGF, or PDGF. The added growth factors include bFGF. The serum free medium supports expansion for at least 20 passages. ACTIVITY - Osteopathic; Gastrointestinal-Gen.; Cardiovascular-Gen.; Nephrotropic; Neuroprotective; Hepatotropic. No biological data given.MECHANISM OF ACTION - None given. USE - The umbilicus-derived cell is useful for therapeutic application in vitro or in vivo. It can be used for treatment of %bone% disease or injury, pancreatic disease or injury, kidney disease or injury, neural disease or injury, cardiac disease or injury, and hepatic disease or injury. It can also be used for producing therapeutic cell or cultures of implanting or grafting. EXAMPLE - The tissue was digested in either DMEM-Low glucose medium or DMEM-High glucose medium. The conical tubes containing the tissue, medium, and digestion enzymes were incubated at 37degreesC in an orbital shaker at 225 rpm for 2 hours. After digestion, the tissues were centrifuged at 150xg for 5 minutes, the

supernatant was aspirated. The pellet was resuspended in 20 milliliters of Growth Medium. The cell suspension was filtered through a 70-micron nylon BD FALCON Cell Strainer. An additional 5 milliliters rinse comprising Growth Medium was passed through the strainer. The cell suspension was then passed through a 40-micrometer nylon cell strainer and chased with a rinse of an additional 5 milliliters of Growth Medium. The filtrate was resuspended in Growth Medium (total volume 50 milliliters) and centrifuged at 150xg for 5 minutes. The supernatant was aspirated and the cells were resuspended in 50 milliliters of fresh growth medium. After the final centrifugation, supernatant was aspirated and the cell pellet was resuspended in 5 milliliters of fresh growth medium. The number of viable cells was determined using Trypan blue staining. Cells were then cultured under standard conditions. The cells isolated from umbilical cord tissues were seeded at 5000 cells/cm2 onto gelatin-coated T-75 flasks in Growth Medium.(81 pages)

2/7/71 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0403988 DBR Accession No.: 2006-17484 PATENT
Treating acute neurodegenerative condition e.g. stoke, comprises administering to the patient postpartum-derived cells from human placental or umbilical cord tissue - human engineered cell culture and differentiation for disease therapy and tissue engineering
AUTHOR: MESSINA D J; MISTRY S; HONG L S K; KRAMER B C; ROMANKO M J; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2006
PATENT NUMBER: WO 200671802 PATENT DATE: 20060706 WPI ACCESSION NO.: 2006-472748 (200648)
PRIORITY APPLIC. NO.: US 638966 APPLIC. DATE: 20041223
NATIONAL APPLIC. NO.: WO 2005US46880 APPLIC. DATE: 20051222
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Treating a patient having an acute neurodegenerative condition comprises administering to the patient postpartum-derived cells in an amount to treat the neurodegenerative condition, where the postpartum-derived cells are derived from human placental or umbilical cord tissue substantially free of blood. DETAILED DESCRIPTION - Treating a patient having an acute neurodegenerative condition by administering postpartum-derived cells, derived from human placental or umbilical cord tissue substantially free of blood, capable of self-renewal and expansion in culture and having the potential to differentiate into cells of a neural phenotype, where the cells require L-valine for growth and can grow in 5% oxygen, and further comprise: (i) potential for 40 doublings in culture; (ii) attachment and expansion on a coated or uncoated tissue culture vessel comprising a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; (iii) production of tissue factor, vimentin, and/or alpha-smooth muscle actin; (iv) production of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and/or HLA-A, B, C; (v) lack of production of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and/or HLA-DR,DP,DQ, as detected by flow cytometry; (vi) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for a gene encoding: interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; tumor necrosis factor, alpha-induced protein 3; C-type lectin superfamily member 2; Wilms tumor 1; aldehyde dehydrogenase 1 family member A2; renin; oxidized low density lipoprotein receptor 1; Homo sapiens clone EVIAGE:4179671; protein kinase C zeta; hypothetical protein DKFZp564F013; downregulated in ovarian cancer 1; and/or Homo sapiens gene from clone DKFZp547kl 113; (vii) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for a gene encoding: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); H. sapiens mRNA; cDNA DKFZpS86M2022 (from clone DKFZpS86M2022); mesenchyme homeo box 2 (growth arrest-specific homeo box); sine oculis homeobox homolog l (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZPS86B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; cholesterol 25-hydroxylase; runt-related transcription factor 3; %interleukin% %11% receptor, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36kDa; H. sapiens cDNA FLJ12280 fis, clone MAMMAIOO1744; cytokine receptor-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, beta 7; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAAI034 protein; vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; early growth response 3; distal-less homeo box 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; transcriptional co-activator with PDZ-%binding% motif (TAZ); fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); H. sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; K IAA0367 protein; natriuretic %peptide% receptor C/guanylate cyclase C (atrionatriuretic %peptide% receptor C); hypothetical protein FLJ14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); similar to neuralin 1; B cell translocation gene 1; hypothetical protein FLJ23191; and/or DKFZp586L151; (viii) secretion of MCP-I, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIPIa, RANTES, and/or TEVIP1; and (ix) lack of secretion of TGF-beta2, ANG2, PDGFbb, MIPIb, 1309, MDC, and/or VEGF, as detected by ELISA. An INDEPENDENT CLAIM is also included for a pharmaceutical composition, for treating a patient having an acute neurodegenerative condition. BIOTECHNOLOGY - Preferred Method: The acute neurodegenerative condition results from ischemic stroke or hemorrhagic stroke. The cells are induced in vitro to differentiate into a neural lineage cells prior to administration. The cells are genetically engineered to produce a gene product that promotes treatment of the neurodegenerative condition. The cells are administered with at least one other cell type, where the other cell type is an astrocyte, oligodendrocyte, neuron, neural progenitor, neural stem cell, genetically engineered cell, or other multipotent or pluripotent stem cell, and where the at least one other cell type is administered simultaneously with, or before, or after, the postpartum-derived cells. The cells are administered with at least one other agent, where the at least one other agent is administered simultaneously with, or before, or after, the postpartum-derived cells. The cells are administered encapsulated within an implantable device. The cells are administered by implantation of a matrix or scaffold containing the cells. The cells are administered at a pre-determined site in the central or peripheral nervous system of the patient. The cells exert a trophic effect on the nervous system of the patient. Alternatively, the method comprises administering to the patient a preparation made from the postpartum-derived cells described in an amount to treat the neurodegenerative condition, where the preparation comprises a cell lysate of the postpartum-derived cells, an extracellular matrix of the postpartum-derived cells, or a conditioned medium in which the postpartum-derived cells were grown. Treating stroke in a patient comprises administering to the patient a therapeutic amount of a cell preparation, where the cell preparation comprises isolated postpartum-derived cells described. The cell preparation further comprises at least one other cell type stated. The cell preparation further comprises at least one other agent. The cell preparation comprises unfractionated cell lysate or membrane-free cell lysate. The cell preparation is formulated for administration by injection or infusion. The cells are encapsulated within an implantable device. The cell preparation is contained within a matrix or scaffold. Preferred Composition: The pharmaceutical composition comprises: (i) a

pharmaceutical carrier and postpartum-derived cells described, in an amount to treat the neurodegenerative condition; or (ii) a pharmaceutical carrier and a preparation made from the postpartum-derived cells, where the preparation comprises a cell lysate of the postpartum-derived cells, an extracellular matrix of the postpartum-derived cells or a conditioned medium in which the postpartum-derived cells were grown. The pharmaceutical composition comprises at least one other cell type given. ACTIVITY - Neuroprotective; Cerebroprotective; Vasotropic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The method and composition are useful for treating an acute neurodegenerative condition, e.g. stroke (cerebrovascular ischemia; claimed). ADMINISTRATION - Administration is by injection or infusion (claimed). No dosage given.(143 pages)

2/7/72 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0403987 DBR Accession No.: 2006-17483 PATENT
New isolated umbilicus-derived cell, capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, for treating e.g. %bone% or kidney disease - mammal cell culture and differentiation for tissue engineering and disease therapy
AUTHOR: HARRIS I R; MESSINA D J; KIHM A; SEYDA A; COLTER D
PATENT ASSIGNEE: ETHICON INC 2006
PATENT NUMBER: WO 200671794 PATENT DATE: 20060706 WPI ACCESSION NO.: 2006-472747 (200648)
PRIORITY APPLIC. NO.: US 639088 APPLIC. DATE: 20041223
NATIONAL APPLIC. NO.: WO 2005US46851 APPLIC. DATE: 20051222
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated umbilicus-derived cell comprises a cell derived from mammalian umbilical cord tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a cell culture comprising the isolated cell, which is free of maternal cells; (2) a therapeutic cell culture comprising the isolated cells; (3) a method of deriving, from umbilical tissue, an isolated cell, the cell capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes; (4) an isolated human umbilicus-derived cell derived by the method of (3); (5) a therapeutic culture of human umbilicus-derived cells derived by the method of (3), where the culture is free of maternal cells; (6) a conditioned culture medium generated by the growth of the culture of (5); (7) a mammalian cell culture comprising the conditioned medium of (6) and a mammalian cell in need of monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, IL-8, granulocyte chemotactic protein (GCP)-2, hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), fibroblast growth factor (FGF), heparin-%binding% epidermal growth factor-like growth factor (HB-EGF), brain-derived neurotrophic factor (BDNF), thrombopoietin (TPO), or tissue inhibitor of metalloproteinase (TIMP)1; (8) a three dimensional matrix comprising the umbilicus-derived cell;(9) an implantable tissue structure comprising the matrix; (10) an implantable device comprising the therapeutic cell; (11) an implantable human tissue matrix comprising the cell; (12) a human tissue comprising the cell; (13) a cell lysate derived from the cell; (14) a %soluble% cell fraction derived from the cell; (15) a membrane-enriched cell fraction derived from the cell; (16) an extracellular membrane fraction derived from the cell; (17) an injectable therapeutic cell comprising an isolated human umbilicus-derived cell; (18) a method for the preparation of therapeutic cells or cultures; (19) a serum-free medium for the expansion of postpartum-derived cells, where the medium has one or more growth factors added; (20) a therapeutic culture comprising postpartum-derived cells expanded in serum-free medium; and (21) a cell culture bank comprising the cells. BIOTECHNOLOGY - Preferred Cell: The isolated cell can expand in the presence of oxygen from 5-20%. It also requires L-valine for growth. The cell can double sufficiently to generate yields of greater than 1014 cells in less than 80 days in culture when seeded at 103 cells/cm2. The cells can double sufficiently to generate greater than 1015 cells in less than 80 days in culture when seeded at 5x103 cells/cm2. The cells can double sufficiently to generate greater than 1017 cells in less than 65 days in culture when seeded at 5x103 cells/cm2. Preferably, the cells can undergo at least 40 doublings in culture. The cell is isolated from human umbilicus. It is isolated in the presence of one or more enzyme activities comprising metalloproteases, neutral proteases, or mucolytic enzymes. The enzyme activities include at least one collagenase, and one or more of the protease activities, dispase, and mermolysin. The enzyme activities are also collagenase from Clostridium histolyticum and dispase. The enzyme activities further include hyaluronidase. The cell attaches and expands on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating with gelatin, laminin, collagen, polyornithine, polylysine, vitronectin, or fibronectin. The cell expands in the presence of 2-15% added serum, in the presence or absence of beta-mercaptoethanol, and in the presence or absence of added growth factors including epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), or leukemia inhibitory factor (LIF). The isolated cell also maintains a normal karyotype as it is passaged. It is characterized in its production or lack of production of one or more cell surface markers comprising CD10, CD13, CD31, CD44, CD45, CD73, CD90, CD117, CD141, PDGFr-alpha, HLA-A5B5C, and HL-DR,DP,DQ. The cell produces one or more of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, or HLA-A,B,C. Alternatively, it produces each of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, and HLA-A,B,C. The cell does not produce one or more of CD31, CD34, CD455 CD117, CD141, or HLA-DR,DP,DQ, as detected by flow cytometry. Specifically, an isolated CD45 umbilicus-derived cell having a cell surface marker profile, produces one or more of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, or HLA-A,B,C, and does not express one or more of CD31, CD34, CD117, CD141, or HLA-DR,DP,DQ, as detected by flow cytometry. The cell surface marker expression profile remains substantially unchanged with passage, culture vessel surface coating, or isolation procedure. The isolated cell expresses a gene for one or more, or each of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; or tumor necrosis factor, alpha-induced protein 3. Preferably, the expression is increased relative to that of a human cell, which is a fibroblast, a mesenchymal stem cell, an ileac crest %bone% marrow cell, or placenta-derived cell. The isolated cell, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, has reduced expression of one or more, or each of the genes selected from short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); Homo sapiens mRNA; cDNA DKFZpS86M2022 (from clone DKPZpS86M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase,

type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); H. sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36 kDa. The isolated cell expresses a gene for one or more, or for each of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; or tumor necrosis factor, alpha-induced protein 3, where the expression is increased relative to that of a human cell which is a fibroblast, a mesenchymal stem cell, an ileac crest %bone% marrow cell, or placenta-derived cell. Alternatively, an isolated human umbilicus-derived cell, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, has reduced expression of genes for each of: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); H. sapiens mRNA; cDNA DKFZpS86M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog I (Drosophila), crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1, potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); H. sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36 kDa; and which expresses a gene for each of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3, where the expression is increased relative to that of a human cell which is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell. The isolated cell is capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes. The isolated cell produces one or both of vimentin and alpha smooth muscle actin, where production of vimentin and alpha smooth muscle actin is retained over passaging under growth conditions. Alternatively, an isolated human umbilicus-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, does not substantially stimulate naive CD4+ T cells, and expresses PD-L2, but not HLA-G, CD 178, HLA-DR, HLA-DP, HLA-DQ, CD80, CD86, or B7-H2. The cell also secretes one or more, or each of the cellular factors MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1. The cell does not secrete one or more of the cellular factors SDF-1alpha, TGF-beta2, ANG2, PDGFbb or VEGF, as detected by ELISA. Alternatively, an isolated human umbilicus-derived cell secretes one or more of the factors MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1, and does not secrete one or more of the factors SDF-1alpha, TGF-beta2, ANG2, PDGFbb or VEGF, as detected by ELISA. Specifically, an isolated postpartum-derived cell comprises an L-valine-requiring cell derived from human postpartum tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into a cell of cardiomyocyte phenotypes; the cell capable of growth in an atmosphere containing oxygen from 5-20%; where the cell comprises at least one of the following characteristics: potential for at least 40 doublings in culture; attachment and expansion on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; production of at least one of tissue factor, vimentin, and alpha-smooth muscle actin; production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2, and HLA-A,B,C; lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR3DP3DQ, as detected by flow cytometry; expression of at least one of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3; expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); H. sapiens mRNA; cDNA DKFZp586M2022 (from clone DKFZpS86M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; H. sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila), KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); H. sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; H. sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36 kDa; secretion of at least one of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIP1a, RANTES, and TIMP1; and lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MIP1beta, 1309, MDC, and VEGF, as detected by ELISA. Specifically, an isolated postpartum-derived cell comprises a signature gene profile where mRNA from genes for reticulon, oxidized LDL %receptor% , and IL-8 are present independent of whether the cells are

grown in medium containing serum or medium free of serum. The isolated postpartum-derived cell further comprises the ability to alter its expression of cell surface markers when grown in medium containing serum relative to that in serum free medium. The markers for PDGF-%receptor% alpha and HLA-ABC are altered. The injectable cell is treated to inactivate tissue factor. It is treated with an anti-tissue factor antibody. Preferred Cell Culture: The therapeutic cell culture does not substantially stimulate allogeneic PBMCs. It also lacks detectable amounts of HLA-DR, HLA-DP, HLA-DQ, CD80, CD86, and B7-H2, as determined by flow cytometry. The therapeutic cell culture further lacks detectable amounts of HLA-G and CD178, as determined by flow cytometry. The therapeutic cell culture produces detectable amounts of PD-L2, as determined by flow cytometry. The therapeutic cell culture does not substantially stimulate a lymphocyte-mediated response in vitro, as compared to allogeneic controls in a mixed lymphocyte reaction. The therapeutic cell culture further comprises one or more of a carrier, another cell culture, an antiapoptotic compound, an antithrombogenic compound, an anti-inflammatory compound, an immunosuppressive compound, an immunomodulatory compound, an angiogenic factor, and a neurotrophic factor. The culture comprises the umbilicus-derived cells and another mammalian cell of any phenotype. It also comprises a human cell line in addition to the umbilicus-derived cell. The therapeutic culture also comprises cells having a signature gene profile, where mRNA from genes for reticulon, oxidized low density lipoprotein (LDL) %receptor% , and IL-8 are present independent of whether the cells are grown in medium containing serum or medium free of serum. Preferred Method: Deriving, from umbilical tissue, an isolated cell, the cell capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes, comprises: (a) obtaining umbilical tissue; (b) removing substantially all of blood to yield a substantially blood-free umbilical tissue; (c) dissociating the tissue by mechanical or enzymatic treatment, or both; (d) resuspending the tissue in a culture medium; and (e) providing growth conditions, which allow for the growth of an umbilicus-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes. The method further comprises selecting adherent cells after 10-100 hours in culture. Preferably, the umbilicus tissue is from a human. The derived cell is capable of expansion in the absence of added growth factors in medium with 2-15% added serum. It can also expand in the presence of oxygen from 5-20%. The derived cell cannot be maintained in the absence of L-valine. It can also undergo at least 40 doublings in culture. The derived cell can double sufficiently to generate at least 1017 cells in less than 65 days in culture when seeded at 5x103 cells/cm2. The umbilical tissue is also obtained after normal or surgically assisted childbirth from a full-term or pre-term pregnancy. Dissociation comprises the use of one or more enzyme activities selected from metalloprotease, hyaluronidase, and neutral protease. Dissociating also comprises incubating at 37degreesC, for one or more hours, preferably 2 hours. The derived cell attaches and expands on a coated or uncoated tissue culture vessel, where the coated tissue culture vessel comprises a coating with gelatin, laminin, collagen, polyornithine, polylysine, vitronectin, or fibronectin. Preferably, it expands in the presence of 2-15% Fetal Bovine Serum, in the presence or absence of beta-mercaptoethanol, and in the presence or absence of one or more added growth factors including EGF, FGF, PDGF, VEGF, IGF, or LIF. Removing comprises removal of free or clotted blood by one or more of washing, suctioning, blotting, centrifugal separation, or enzymatic removal. Preferably, the dissociating is accomplished aseptically. Dissociation comprises one or more of mincing, blending, homogenizing, or grinding. Preparing therapeutic cells or cultures comprises: (a) isolating cells; (b) initially expanding the cells to a useful number in a serum-containing medium, which supports cell expansion but in which the cells produce a quantity of the cell surface marker HLA-ABC; (c) transferring the cells to a medium in which the cells produce a decreased amount of the cell surface marker HLA-ABC; and (d) passaging the cells in the medium in which the cells produce a decreased amount of the HLA-ABC, thus preparing a therapeutic cell or culture. The medium in which the cells produce a decreased amount of the cell surface marker HLA-ABC is a serum-free medium. The method is for the production of therapeutic cells or cultures for implantation or grafting. Preferred Three-Dimensional Matrix: The matrix comprises a biocompatible or bioabsorbable polymer. The matrix comprises PGA/PLA copolymer, PCL/PGA copolymer, or self-assembling %peptides% . Preferred Medium: The conditioned medium comprises one or more of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, or TIMP1. In the serum-free medium, the one or more growth factors added are basic fibroblast growth factor (bFGF), EGF, or PDGF. The serum free medium supports expansion for at least 20 passages. ACTIVITY - Osteopathic; Gastrointestinal-Gen.; Nephrotropic; Neuroprotective; Cardiant; Hepatotropic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The umbilicus-derived cells and methods are useful in producing therapeutic cells and cultures for implantation and grafting. The cells can be used for treating %bone%, pancreatic, kidney, neural, cardiac, or hepatic disease or injury. ADMINISTRATION - Administration is by implantation.(185 pages)

2/7/73 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

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New stem cell comprising a self-replicating artificial chromosome comprising a neocentromere having centromeric chromatin domains, useful for tissue repair, replacement, rejuvenation and/or augmentation therapy - self-replicating artificial chromosome-containing stem cell for cell therapy and gene therapy
AUTHOR: CHOO K A; WONG L H; SAFFERY R E
PATENT ASSIGNEE: MURDOCH CHILDRENS RES INST 2005
PATENT NUMBER: WO 200540391 PATENT DATE: 20050506 WPI ACCESSION NO.: 2005-322966 (200533)
PRIORITY APPLIC. NO.: AU 2003905894 APPLIC. DATE: 20031027
NATIONAL APPLIC. NO.: WO 2004AU1469 APPLIC. DATE: 20041025
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A stem cell comprising a self-replicating artificial chromosome comprising a neocentromere having centromeric chromatin domains, where the artificial chromosome comprises expressible genetic material within the centromeric chromatin domains or in a region proximal thereto which modifies or introduces at least one trait in the stem cell, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a method of modulating the genetic potential of a stem cell; (2) a method for directing differentiation, proliferation or self-renewal of a stem cell; (3) a method for altering the genetic potential of a stem cell or its daughter cell; (4) an isolated nucleic acid molecule comprising a nucleotide sequence corresponding to a neocentromeric region of human DNA and having a centromeric chromatin domain, the nucleic acid molecule further comprising a second nucleic acid molecule inserted within the centromere chromatin domain or immediately adjoining or proximal region and which second nucleic acid molecule is expressible and where the expression product alters the genetic potential of a stem cell or its daughter cells where the neocentromeric region comprises a q and p arm domain, CENP-H, HP1 domain and a scaffold domain and comprises a gene selected from but not limited to hCG41809, hCG40976, hCG1811152, hCG1781464, hCG39839, hCG1781461, hCG40945, hCG1818126, hCG1811159, hCG409445 hCG40949, hCG39837, hCG40963, hCG40964; (5) a method differentiating a stem cell; and (6) a method of treating a subject therapeutically or prophylactically. BIOTECHNOLOGY - Preferred Stem Cell: The stem cell is selected from embryonic stem cells, somatic stem cells, germ stem cells, epidermal stem cells, adult neural stem cells, keratinocyte stem cells, melanocyte stem cells, adult renal stem cells, embryonic renal epithelial stem cells, embryonic endodermal stem cells, hepatocyte stem cells, mammary epithelial stem cells, bane marrow-derived stem cells, skeletal muscle stem cells, %bone% marrow mesenchymal stem cells, CD34+ hematopoietic stem cells, mesenchymal stem cells. The stem cell differentiates into a cell selected from keratinocytes, fibroblasts, pancreatic islets, pancreatic beta-cells, kidney epithelial cells, hepatocytes, bile duct epithelial cells, lung

fibroblasts, bronchial epithelial cells, alveolar type II pneumocytes, cardiomyocytes, simple squamous epithelial cells, descending aortic endothelial cells, aortic arch endothelial cells, aortic smooth muscle cells, corneal epithelial cells, osteoblasts, peripheral blood mononuclear progenitor cells, osteoclasts, stromal cells, splenic precursor cells, splenocytes, CD4+ T-cells, CD8+ T-cells, NK cell, monocytes, macrophages, dendritic cells, B-cells, goblet cells, pseudostriated ciliated columnar cells, pseudostratified ciliated epithelium, stratified epithelial cells, ciliated columnar cells, basal cells, cricopharyngeus muscle cells. The genetic material corresponds to a DNA sequence encoding a cytokine, growth factor or receptor selected from Activin RIA (Activin Receptor), ADAM (A Desintegrin and Metalloprotease-like Domain), ADAMTS (A Disintegrin-like and Metalloproteinase Domain with Thrombospondin Type I Motifs), ALCAM (Activated Leukocyte Cell Adhesion Molecule), ALK (Activin Receptor-like Kinase) ANG (Angiogenin), Ang (CC Chemokine Receptors), APAF-1 (Apoptosis Protease Activating Factor-1), APE (AP Endonuclease), APJ (A Seven Transmembrane-domain Receptor), APP (Amyloid Precursor Protein), APRIL (a Proliferation-inducing Ligand), AR (Amphiregulin), ARC (Agouti-related Transcript), ART (Fibroblast Growth Factor), Axl (a Receptor Tyrosine Kinase), beta2M (beta2 Microglobulin), B7-H (B7 Homolog), BACE (beta-site APP Cleaving Enzyme), Bad (Bc1-xL/Bc1-2 Associated Death Promoter), BAFF (B cell Activating Factor), Bag-1 (Bc1-2-associated Anthanogene-1), BAK (Bc1-2 Antagonist/Killer), Bax (Bc1 Associated X Protein), BCA-1 (B-Cell-attracting Chemokine 1), BCAM (Basal-cell Adhesion Molecule), Bc1 (B-Cell Lymphoma/Leukemia), BCMA (B Cell Maturation Factor), BDNF (Brain-derived Neurotrophic Factor), beta-ECGF (beta Endothelial Cell Growth Factor), BID (BH3 Interacting Domain Death Agonist), Bik (Bc1-2 Interacting Killer), BIM (Bc1-2 Interacting Mediator of Cell Death), BLC (B-Lymphocyte Chemoattractant), BL-CAM (B-lymphocyte Cell Adhesion Molecule), BLK (Bik-like Killer Protein), BMP (%Bone% Morphogenetic Protein), BMPR (%Bone% Morphogenetic Protein Receptor), beta-NGF (beta Nerve Growth Factor), BOK (Bc1-2-related Ovarian Killer), BPDE (Benzo(a)Pyrene-Guanosine-BSA), BPDE-DNA (Benzo(a)Pyrene-Diol Epoxide-D NA), BTC (beta cellulin), C10 (a Novel Mouse CC Chemokine), CAD-8 (Cadherin-8), cAMP (Cyclic AMP), Caspase (Caspase-1), CCI (CC Chemokine Inhibitor), CCL (CC Chemokine Ligands), CCR (CC Chemokine Receptors), CD (Cluster of Differentiation), CD30L (CD30 Ligand), CD40L (CD40 Ligand), CFTR (Cystic Fibrosis Transmembrane Conductance Regulator), cGMP (Cyclic GMP), CINC (Cytokine-induced Neutrophil Chemotactic Factor), CKbeta8-1 (Chemokine beta 8-1), CLC (Cardiotrophin-like Cytokine), CMV UL (Cytomegalovirus ORFUL), CNTF (Ciliary Neurotrophic Factor), CNTN-1 (Contactin-1), COX (Cyclooxygenase), C-Ret (a Receptor Tyrosine Kinase), CRG-2 (a Mouse CXC Chemokine), CT-1 (Cardiotrophin 1), CTACK (Cutaneous T-cell Attracting Chemokine), CTGF (Connective Tissue Growth Factor), CTLA-4 (Cytotoxic T-lymphocyte-associated Molecule 4), CXCL (CXC Chemokine Ligands), CXCR (CXC Chemokine Receptors), DAN (Differential Screening-selected Gene Aberrant in Neuroblastoma), DCC (Deleted in Colorectal Cancer), DcR3 (Decoy Receptor 3), DC-SIGN (Dendritic Cell-specific ICAM-3-grabbing Nonintegrin), Dhh (Desert Hedgehog), DNAM-1 (DNAX Accessory Molecule 1), Dpp (Decapentaplegic), DR (Death Receptor), Dtk (Developmental Tyrosine Kinase), ECAD (E-Cadherin), EDA (Ectodysplasin-A), EDAR (Ectodysplasin Receptor), EGF (Epidermal Growth Factor), EMMPRIN (Extracellular Matrix Metalloproteinase Inducer, CD 147), ENA (Epithelial-derived Neutrophil Attractant), eNOS (Endothelial Nitric Oxide Synthase), Eot (Eotaxin Epo Erythropoietin), ErbB3 (Erb B3 Receptor Protein Tyrosine Kinase), ERCC (Excision Repair Cross-complementing), ET-1 (Endothelin-1), Fas (Fibroblast-associated), FEN-1 (Flap Endonuclease), FGF (Fibroblast Growth Factor), FL (Fas Ligand FasL), FLIP (FLICE Inhibitory Proteins), Flt-3 (fins-like Tyrosine Kinase 3), Fractalkine, Gas 6 (Growth-arrest-specific Protein 6), GCP-2 (Granulocyte Chemotactic Protein 2), G-CSF (Granulocyte Colony Stimulating Factor), GDF (Growth Differentiation Factor), GDNF (Glial cell line-derived Growth Factor), GFAP (Glial Fibrillary Acidic Protein), GFRa-1 (Glial Cell Line-derived Neurotropic Factor Receptor a 1), GITR (Glucocorticoid Induced TNF Receptor Family Related Gene), Glut 4 (Insulin Regulated Glucose Transporter Protein), GM-CSF (Granulocyte Macrophage Growth Factor), gp130 (glycoprotein 130), GRO (Growth Related Protein a), HB-EGF (Heparin %Binding% Epidermal Growth Factor), HCC (Hemofiltrate CC Chemokine), HCMV UL (Human Cytomegalovirus ORFUL), HGF (Hepatocyte Growth Factor), HRG (Heregulin), Hrk (Harakiri HVEM Herpes virus Entry Mediator), I-309 (a human CC chemokine), IAP (Inhibitors of Apoptosis), ICAM (Intercellular Adhesion Molecule, ICOS (Inducible Co-stimulator), IFN (Interferon Ig Immunoglobulin), IGF (Insulin-like Growth Factor), IGFBP (Insulin-like Growth Factor %Binding% Protein), IL-1a (hInterleukin-1a), hIL-1b (Interleukin-lb), hIL-2(Interleukin-2), hIL-3 (Interleukin-3), hIL-4 (Interleukin-4), WL-5 (Interleukin-5), hIL-6 (Interleukin-6), hIL-7 (Interleukin-7), ML-IO (Interleukin-10), hIL-11 (%Interleukin%-%11%), hIL-12 (Interleukin-12), hIL-13 (Interleukin-13), hIL-15 (Interleukin-15), hIL-18 (Interleukin-18), iNOS (Inducible Nitric Oxide Synthase), IP-10 (Interferon gamma Inducible Protein 10), I-TAC (Interferon-inducible T-cell a Chemoattractant), JE (Mouse homologue of human MCP-I), KC (Mouse homologue of human GRO), KGF (Keratinocyte Growth Factor), LAMP (Limbic System-associated Membrane Protein), LAP (Latency-associated %Peptide%), LBP (Lipopolysaccharide-%binding% Protein), LDGF (Leukocyte-derived Growth Factor), LECT2 (Leukocyte Cell-Derived Chemotaxin 2), LFA-1 (Lymphocyte Function-associated Molecule-1Lfo), Lfo (Lactoferrin), LIF (Leukemia Inhibitory Factor), LIGHT (Name derived from Homologous to Lymphotoxins, Inducible expression, competes with HSV Glycoprotein D for HVEM, a receptor expressed on T-lymphocytes), LIX (LPS-induced CXC Chemokine), LKN (Leukotactin), Lptn (Lymphotactin), LT-alpha (Lymphotoxin a (aka TNF-alpha)), LT-beta (Lymphotoxin beta (aka p33)), LTB4 (Leukotriene B4), LTBP-1 (Latent TGF-beta bp1), MAG (Myelin-associated Glycoprotein), MAP2 (Microtubule-associated Protein 2), MARC (Mast Cell Activation-Related Chemokine), MCAM (Melanoma Cell Adhesion Molecule (aka MUC 18, CD 146)), MCK-2 (Mouse Cytomegalovirus Viral CC Chemokine Homolog 2), MCP (Monocyte Chemotactic Protein), M-CSF (Macrophage Colony Stimulating Factor), MDC (Macrophage-derived Chemokine (aka STP-I)), Mer (Tyrosine Protein Kinase), MGMT (O-6 Methylguanine-DNA Methyltransferase), MIF (Macrophage Migration Inhibitory Factor), MIG (Monokine Induced by IFN-g), MIP (Macrophage Inflammatory protein), MK (Midkine), MMACI (Mutated in Multiple Advanced Cancers Protein 1), MMP (Matrix Metalloproteinase), MPIF (Myeloid Progenitor Inhibitory Factor), Mpo (Myeloperoxidase), MSK (Mitogen- and Stress-activated Protein Kinase), MSP (Macrophage Stimulating Protein), Mug (Mismatch Uracil DNA Glycosylase), MuSK (Muscle-specific Kinase), NAIP (Neuronal Apoptosis Inhibitor Protein), NAP (Neutrophil Activation Protein), NCAD N-Cadherin (N-Cadherin Neural Cadherin), NCAM (Neural Cell Adhesion Molecule), nNOS (Neuronal Nitric Oxide Synthase), NO (Nitric Oxide), NOS (Nitric Oxide Synthase), Npn (Neuropilin), NRG-3 (Neuregulin-3), NT (Neurotrophin), NTN (Neurturin), OB (Leptin, product of the ob gene), OGG1 (8-oxoGuanine DNA Glycosylase), OPG (Osteoprotegerin), OPN (Osteopontin), OSM (Oncostatin M), PADPr (Poly (ADP-ribose) Polymer), PARC (Pulmonary and Activation-regulated Chemokine), PARP (Poly (ADP-ribose) Polymerase), PBR (Peripheral-type Benzodiazepine ReceptorInterleukin-1a (hIL-1a), Interleukin-1b (hIL-1b), Interleukin-2 (hIL-2), Interleukin-3 (hIL-3), Interleukin-4 (hIL-4), Interleukin-5 (hIL-5), Interleukin-6 (hIL-6), Interleukin-7 (hIL-7), Interleukin-10 (hIL-10), %Interleukin%-%11% (ML-11), Interleukin-12 (hIL-12), Interleukin-13 (hIL-13), Interleukin-15 (hIL-15), Interleukin-18 (hIL-18), PBSF (Pre-B Cell Growth Stimulating Factor (aka SDF-1)Interleukin-1a (hIL-1a), Interleukin-1b (hIL-1b), Interleukin-2 (hIL-2), Interleukin-3 (hIL-3), Interleukin-4 (hIL-4), Interleukin-5 (hIL-5), Interleukin-6 (hIL-6), Interleukin-7 (hIL-7), Interleukin-10 (hIL-10), %Interleukin%-%11% (hIL-11), Interleukin-12 (hIL-12), Interleukin-13 (hIL-13), Interleukin-15 (hIL-15), Interleukin-18 (hIL-18), PCAD (P-Cadherin Placental Cadherin), PCNA (Proliferating Cell Nuclear Antigen), PDGF (Platelet-derived Growth Factor), PDK-1(Phosphoinositide Dependent Kinase-1), PECAM (Platelet Endothelial Cell Adhesion Molecule), PF4 (Platelet Factor 4), PGE (Prostaglandin E), PGF (Prostaglandin F), PGJ2 (Prostacyclin PGJ2 Prostaglandin J2), PIN (Protein Inhibitor of Neuronal Nitric Oxide Synthase), PLA2 (Phospholipase A2), P1GF (Placenta Growth Factor), PLP (Proteolipid Protein), PP14 (Placental Protein 14), PS (Presenilin), PTEN (Protein Tyrosine Phosphatase and Tensin Homolog, see MMAC PTN Pleiotrophin), R51 (S. cerevisiae homolog of RAD51), RANK (Receptor Activator of

NF-kappa-B), RANTES (Regulated upon activation, normal T cell Expressed and Secreted), Ret (Proto-oncogene Tyrosine-protein Kinase Receptor), RPA2 (Replication Protein A2), RSK (Ribosomal Protein S6 Kinase II), SCF/KL (Stem Cell Factor/KIT Ligand), SDF-1 (Stromal Cell-derived Factor 1 (aka PBSF)), sFRP-3 (Secreted Frizzled Related Protein), Shh (Sonic Hedgehog), SIGIRR (Single Ig Domain Containing IL-1 Receptor-related Molecule), SLAM (Signaling Lymphocytic Activation Molecule), SLPI (Secretory Leukocyte protease Inhibitor), SMAC (Second Mitochondria-derived Activator of Caspase), SMDF (Sensory and Motor Neuron-derived Factor), SOD (Superoxide Dismutase), SPARC (Secreted Protein Acidic and Rich in Cysteine), Stat (Signal Transducer and Activator of Transcription), TACE (TNF-alpha-Converting Enzyme), TACI (Transmembrane Activator and CAML Interactor), TARC (Thymus and Activation-regulated Chemokine), TCA-3 (a CC Chemokine), TECK (Thymus-expressed Chemokine), TERT (Telomerase Reverse Transcriptase), TfR (Transferrin Receptor), TGF (Transforming Growth Factor), Thymus Ck-1 (Thymus Chemokine 1), Tie (Tyrosine Kinase with Immunoglobulin and Epidermal Growth Factor Homology Domains), TIMP (Tissue Inhibitors of Metalloproteinases) TIQ (N-methyl-6,7-dihydroxytetrahydroisoquinoline), Tmpo (Thymopoietin), TNF-R (TNF- Receptor), TNF (Tumor Necrosis Factor), TP-1 (Trophoblast Protein-1), Tpo (Thrombopoietin), TRAIL (TNF-related Apoptosis-inducing Ligand), TRAIL R (TRAIL Receptor), TRANCE (TNF-related Activation-induced Cytokine), TRF (Telomeric Repeat %Binding% Factor), Trk (Neurotrophic Tyrosine Kinase Receptor), TROP-2 (Tumor Associated Calcium Signal Transducer), TSG (Twisted Gastrulation), TSLP (Thymic Stromal Lymphopoietin), TWEAK (TNF-like and Weak Inducer of Apoptosis), TXB2 (Thromboxane B2), Ung (Uracil-N-Glycosylase), uPAR (Urokinase-type Plasminogen Activator Receptor), uPAR-1 (Urokinase-type Plasminogen Activator Receptor 1), VCAM-1 (Vascular Cell Adhesion Molecule 1), VECAD (VE-Cadherin Vascular Epithelium Cadherin), VEGF (Vascular Endothelial Growth Factor), VEGI (Vascular Endothelial Growth Inhibitor), VIM (Vimentin), VLA-4 (Very Late Antigen-4), WIF-1 (Wnt Inhibitory Factor), XIAP (X-linked Inhibitor of Apoptosis) or XPD (Xeroderma Pigmentosum D). The heterologous DNA sequence encodes a protein selected from Bc1-2, Bc1-w and Bc1-xy, Bc1-2-associated athanogene 1, CCAAT/enhancer %binding% protein (C/EBP), empty spiracles homolog 1 (Drosophila), empty spiracles homolog 2 (Drosophila), forkhead box G1, proprotein convertase subtilisin/kexin type 9, suppressor of cytokine signaling 2, T-cell leukemia, homeobox 1, T-cell leukemia, homeobox 3, insulin-like growth factor 1, neuregulin 1, neurotrophin 5, cut-like 1 (Drosophila), growth factor independent 1, mucolipin 3, mucosal vascular addressin cell adhesion molecule 1, tumor susceptibility gene 101, endothelin 3, endothelin receptor type B and/or a %bone% morphogenetic protein (BMP) such as BMP1, BMP2, BMP3 or BMP4. The artificial chromosome is a human artificial chromosome. Preferred Method: Modulating the genetic potential of a stem cell comprises introducing into the stem cell or a parent of the stem cell an artificial chromosome comprising a neocentromere having centromeric chromatin domains, which comprises expressible genetic material within the centromeric chromatin domains or in region proximal to it, which modifies or introduces at least one trait in the stem cell. Directing differentiation, proliferation or self-renewal of a stem cell comprises introducing into the stem cell or a parent of said stem cell an artificial chromosome comprising a neocentromere having centromeric chromatin domains, which comprises genetic material within the centromeric chromatin domains or in a region proximal to it, which is capable of generating an expression production which modulates stem cell differentiation, proliferation and/or self-renewal. Altering the genetic potential of a stem cell or its daughter cell comprises incorporating into a stem cell or its parent at least one artificial chromosome comprising a neocentromere having centromeric chromatin domains of mammalian, avian or other higher eukaryote DNA origin. Differentiating a stem cell comprises introducing an artificial or engineered chromosome comprising a neocentromere having centromeric chromatin domains of mammalian, avian or plant or higher eukaryote DNA. The method alternatively comprises introducing into a stem cell a mammalian artificial or engineered chromosome comprising a neocentromere having centromeric chromatin domains of mammalian origin. Treating a subject therapeutically or prophylactically comprises administering to the subject a stem cell of Claim 1 or a stem cell generated from the method cited above. The subject is a human. ACTIVITY - Immunosuppressive. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The stem cells are useful for tissue repair, replacement, rejuvenation and/or augmentation therapy, e.g. for treating patients requiring organ transplantation. EXAMPLE - Mouse F9 teratocarcinoma cells, human HCT116, human 293T and mouse ES cell derivatives were cultured in Dulbeccos Modified Eagles Medium supplemented with 10% v/v FCS, penicillin, streptomycin. Growth medium for mouse ES lines was supplemented with leukemia-inhibitory factor (LIF) and (beta-mercaptoethanol). CHO cell lines and derivative somatic cell hydrids were cultured Ham's F12 medium supplemented with 200 microg/ml zeocin. All cells were maintained at sub confluency and were split 1:4 at 24 hr prior to RNA isolation to ensure logarithmic growth of harvest.(168 pages)

2/7/74 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0370312 DBR Accession No.: 2005-16018 PATENT
New postpartum-derived cell capable of self-renewal and expansion in culture and that can differentiate into a cell of an osteogenic or chondrogenic phenotype, for diagnosing or treating %bone% or cartilage disorders, e.g. rickets - cell culture medium expansion and differentiation for use in disease therapy and tissue engineering
AUTHOR: KIHM A J; SEYDA A; DHANARAJ S; WANG Z; HARMON A M; HARRIS I R; MESSINA D J; MISTRY S; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200538012 PATENT DATE: 20050428 WPI ACCESSION NO.: 2005-315703 (200532)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20958 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A postpartum-derived cell comprising a cell derived from human postpartum tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of an osteogenic or chondrogenic phenotype, where the cell requires L-valine for growth, and where the cell is capable of growth in about 5-20% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) methods of inducing differentiation of the postpartum-derived cell to a chondrogenic or osteogenic phenotype; (2) the cell produced by (1); (3) a cell population comprising the postpartum-derived cell; (4) a cell lysate prepared from the cell population; (5) a %soluble% cell fraction prepared from the cell lysate; (6) an extracellular matrix of the cell population, or a matrix comprising the cell population; (7) a composition comprising the cell population and one or more bioactive factors; (8) a pharmaceutical composition comprising the cell, extracellular matrix or lysate, and a pharmaceutical carrier; (9) a cell culture comprising the cell in a culture medium; (10) methods of treating a condition in a patient, particularly a patient having a %bone% or cartilage condition; (11) methods of regenerating a tissue in a patient; (12) a conditioned medium generated by the growth of the culture of (9); (13) methods for identifying a compound that stimulates chondrogenesis or osteogenesis of a postpartum-derived cell, or that is toxic to the postpartum-derived cell; (14) a kit comprising at least one new cell and at least one additional component of a matrix, a hydrating agent, a cell culture substrate, a differentiation-inducing agent, and cell culture media. BIOTECHNOLOGY - Preferred Cell: The cell further comprises at least one of the following characteristics: (a) production of at least one of granulocyte chemotactic protein 2 (GCP-2), reticulon 1, tissue factor, vimentin, and alpha-smooth muscle actin; (b) lack of production of at least one of GRO-alpha or oxidized low density lipoprotein %receptor%, as detected by flow cytometry; (c) production of at least one of CD10, CD13, CD44, CD73, CD90, platelet derived growth factor %receptor%-alpha (PDGFr-alpha), programmed-death ligand 2 (PD-L2) and human leukocyte antigen (HLA)-A, B or C; (d) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117,

CD141, CD178, B7-H2, HLA-G, and HLA-DR, DP or DQ, as detected by flow cytometry; (e) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an iliac crest %bone% marrow cell, is increased for at least one of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3 or expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an iliac crest %bone% marrow cell, is increased for at least one of C-type lectin superfamily member A2, Wilms tumor 1, aldehyde dehydrogenase 1 family member A2, renin, oxidized low density lipoprotein %receptor% 1, protein kinase C zeta, clone IMAGE:4179671, hypothetical protein DKFZp564F013, downregulated in ovarian cancer 1, and clone DKFZp547K1113; (f) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an iliac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2; sine oculis homeobox homolog 1; crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin; src homology 3 (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7; hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C; iroquois homeobox protein 5; hephaestin; integrin, beta8; synaptic vesicle glycoprotein 2; cDNA FLJ12280 fis, clone MAMMA 1001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2; KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5; EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36kDa; (g) secretion of at least one of monocyte chemotactic protein-1, interleukin(IL)-6, IL-8, granulocyte chemotactic protein-2, hepatocyte growth factor, keratinocyte growth factor, fibroblast growth factor, heparin %binding%-epidermal growth factor, brain derived neurotrophic factor, thrombopoietin, macrophage inflammatory protein (MIP)-1a, RANTES, and tissue inhibitor of matrix metalloprotease 1; (h) lack of secretion of at least one of transforming growth factor-beta2, angiopoietin-2, platelet derived growth factor-bb, macrophage inflammatory protein 1beta (MIPIb), I309, macrophage-derived chemokine, and vascular endothelial growth factor, as detected by ELISA; and (i) the ability to undergo at least 40 population doublings in culture. The cell has been isolated from a post-partum placenta or its fragment by enzymatic dissociation with at least one of a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid. Preferred Method: Inducing differentiation of the postpartum-derived cell to a chondrogenic phenotype comprises exposing the cell to one or more chondrogenic differentiation-inducing agents. The chondrogenic differentiation-inducing agent comprises at least one of transforming growth factor-beta3 (TGFbeta3) and growth and differentiation factor-5 (GDF-5). The method further comprises culturing the cell in chondrogenic medium, which comprises Dulbecco's modified Eagle's medium, L-glutamine, sodium pyruvate, L-proline, dexamethasone, L-ascorbic acid, insulin, transferrin, selenium, and an antibiotic agent. The chondrogenic medium further comprises at least one of collagen and sodium hydroxide. The method further comprises evaluating differentiation of the cell by a pellet culture assay or by detecting the presence of a glycosaminoglycan or collagen. The step of evaluating comprises staining the cell with Safranin-O or hematoxylin/eosin. Inducing the differentiation of the above postpartum-derived cell to an osteogenic phenotype comprises exposing the cell to one or more osteogenic differentiation-inducing agents. The differentiation-inducin g agent comprises at least one of %bone% morphogenic protein (BMP)-2, BMP-4, and transforming growth factor-beta1. The method further comprises culturing the cell in osteogenic medium comprising Dulbecco's modified Eagle's medium-low glucose, serum, beta-glycerophosphate, dexamethasone, ascorbic phosphate salt, and at least one antibiotic or antimycotic agent. The method further comprises evaluating the differentiation by detecting an osteogenic lineage-specific marker. The marker is osteocalcin, %bone% sialoprotein, or alkaline phosphatase. It further comprises detecting the differentiation by measuring mineralization. The step of detecting comprises von Kossa staining. Treating a condition in a patient comprises administering to the patient one or more postpartum-derived cells mentioned above. The condition is a %bone% or cartilage condition, such as a congenital %bone% or cartilage defect, meniscal injury or defect, %bone%/spinal deformation, osteosarcoma, myeloma, %bone% dysplasia or scoliosis, osteoporosis, periodontal disease, dental %bone% loss, osteomalacia, rickets, fibrous osteitis, renal %bone% dystrophy, spinal fusion, spinal disc reconstruction or removal, Paget's disease of %bone%, rheumatoid arthritis, osteoarthritis, or a traumatic or surgical injury. The postpartum-derived cells are administered with at least one other cell type, such as %bone% marrow cells, chondrocytes, chondroblasts, chondrocyte progenitor cells, osteocytes, osteoblasts, osteoclasts, %bone% lining cells, stem cells, or other pluripotent or multipotent cell. The postpartum-derived cells are inoculated on a matrix that is implanted into the patient. The postpartum-derived cells are induced to differentiate to a chondrogenic or osteogenic phenotype prior to the step of administering. These cells are co-administered with at least one bioactive factor. The cells are administered to a %bone% or a cartilage of the patient. Alternatively, treating a patient having a %bone% or cartilage condition comprises administering to the patient the extracellular matrix of the cell cited above, or the cell lysate or conditioned medium as mentioned above. Regenerating a tissue in a patient comprises administering the cell population cited above to the patient. The tissue is %bone% or cartilage. The cells are implanted into the patient. Identifying a compound that stimulates chondrogenesis or osteogenesis of a postpartum-derived cell comprises contacting the cell cited above with the compound and monitoring the cell for a marker of chondrogenesis or osteogenesis. Identifying a compound that is toxic to the above postpartum-derived cell comprises contacting the cell with the compound and monitoring survival of the cell. Preferred Cell Population: The cell population is substantially homogeneous or heterogeneous. It further comprises at least one cell type of %bone% marrow cells, chondrocytes, chondroblasts, chondrocyte progenitor cells, stem cells, or other pluripotent or multipotent cell. Preferred Composition: The bioactive factor is a chondrogenic or an osteogenic differentiation-inducing factor. The pharmaceutical composition comprises an amount of the cells, extracellular matrix or lysate to treat a %bone% or cartilage condition. The pharmaceutical composition further comprises at least one other cell type of stem cells, %bone% marrow cells, chondrocytes, chondroblasts, osteocytes, osteoblasts, osteoclasts, %bone% lining cells, and other %bone% or cartilage progenitor cells. Preferred Cell Culture: The culture medium comprises chondrogenic medium or osteogenic medium. The cell culture further comprises at least one chondrogenic differentiation-inducing agent. The chondrogenic differentiation-inducing agent is at least one of transforming growth factor-beta1 or growth and differentiation factor-5. It further comprises at least one osteogenic differentiation-inducing agent, such as transforming growth factor-beta1, BMP2 or BMP4. Preferred Matrix: The matrix comprises a 3-dimensional scaffold. Preferred Kit: The matrix is a 3-dimensional scaffold and the cell is seeded on the scaffold. The differentiation-inducing agent is an osteogenic differentiation-inducin g agent or a chondrogenic differentiation-inducing agent. ACTIVITY -

Osteopathic; Cytostatic; Antiarthritic; Antirheumatic; Vulnerary. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The composition and methods are useful for diagnosing or treating %bone% or cartilage disorders, such as a congenital %bone% or cartilage defect, meniscal injury or defect, %bone%/spinal deformation, osteosarcoma, myeloma, %bone% dysplasia or scoliosis, osteoporosis, periodontal disease, dental %bone% loss, osteomalacia, rickets, fibrous osteitis, renal %bone% dystrophy, spinal fusion, spinal disc reconstruction or removal, Paget's disease of %bone% , rheumatoid arthritis, osteoarthritis, or a traumatic or surgical injury. These may also be used in research applications or in screening for agents that may treat the disorders (claimed). ADMINISTRATION - Administration can be intramuscular, ophthalmic, intraarterial, intravenous, subcutaneous, oral, nasal, intraperitoneal, and the like. No dosage given. EXAMPLE - No relevant example given. (146 pages)

2/7/75 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0361580 DBR Accession No.: 2005-07284 PATENT
New postpartum-derived cell, useful for treating a %bone% or cartilage condition, e.g. osteosarcoma, rheumatoid arthritis or osteoarthritis - cell culture and differentiation of a postpartum derived cell useful for a disease cell therapy and a tissue engineering application
AUTHOR: KIHM A J; SEYDA A; DHANARAJ S; WANG Z; HARMON A M; HARRIS I R; MESSINA D J; MISTRY S; GOSIEWSKA A; YI C
PATENT ASSIGNEE: KIHM A J; SEYDA A; DHANARAJ S; WANG Z; HARMON A M; HARRIS I R; MESSINA D J; MISTRY S; GOSIEWSKA A; YI C 2005
PATENT NUMBER: US 20050019865 PATENT DATE: 20050127 WPI ACCESSION NO.: 2005-121299 (200513)
PRIORITY APPLIC. NO.: US 876998 APPLIC. DATE: 20040625
NATIONAL APPLIC. NO.: US 876998 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A postpartum-derived cell (PDC) comprising a cell derived from human postpartum tissue substantially free of blood, is new. DETAILED DESCRIPTION - A postpartum-derived cell (PDC) comprises a cell derived from human postpartum tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of an osteogenic or chondrogenic phenotype, where the cell requires L-valine for growth, where the cell is capable of growth in 5-20 % oxygen, where the cell further comprises: (a) production of at least one of granulocyte chemotactic protein 2 (GCP-2), reticulon 1, tissue factor, vimentin, and alpha-smooth muscle actin; (b) lack of production of at least one of GRO-alpha or oxidized low density lipoprotein %receptor%, as detected by flow cytometry; (c) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and HLA-A,B,C; (d) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR,DP, DQ, as detected by flow cytometry; (e) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for: interleukin 8, reticulon 1, chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha), chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2), chemokine (C-X-C motif) ligand 3, and tumor necrosis factor, alpha-induced protein 3 or expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for at least one of C-type lectin superfamily member A2, Wilms tumor 1, aldehyde dehydrogenase 1 family member A2, renin, oxidized low density lipoprotein %receptor% 1, protein kinase C zeta, clone IMAGE:4179671, hypothetical protein DKFZp564F013, down regulated in ovarian cancer 1, and clone DKFZp547K1113; (f) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell derived factor 1); elastin; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2; sine oculis homeobox homolog 1; crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin, sro homology three (SH3) and cysteine rich domain; B-cell translocation gene 1; antiproliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%; alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7; hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C; iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor I; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2; KIAAI034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5; EGF-containing fibulin-like extracellular matrix protein 1; BCL2/ adenovirus E1B 19 kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36 kDa; (g) secretion of monocyte chemotactic protein-1, interleukin (IL)-6, IL-8, granulocyte chemotactic protein-2, hepatocyte growth factor, keratinocyte growth factor, fibroblast growth factor, heparin %binding%-epidermal growth factor, brain derived neurotrophic factor, thrombopoietin, macrophage inflammatory protein (MIP)-1a, RANTES, and tissue inhibitor of matrix metalloprotease 1; (h) lack of secretion of transforming growth factor-beta2, angiopoetin-2, platelet derived growth factor-bb, MIP1b, 1309, macrophage-derived chemokine, and vascular endothelial growth factor, as detected by ELISA; and (i) the ability to undergo at least 40 population doublings in culture. INDEPENDENT CLAIMS are also included for: (1) inducing differentiation of a PDC to a chondrogenic or an osteogenic phenotype (M1); (2) a cell (I) produced by (M1); (3) a cell population (II) comprising PDC or comprising the cell (I);(4) a cell lysate (III) prepared from the cell population (II); (5) a %soluble% cell fraction prepared from the cell lysate of (III); (6) a(n) (extracellular) matrix (IV) of the cell population of (II); (7) a composition comprising the cell population (II) and one or more bioactive factors; (8) a pharmaceutical composition comprising a PDC or a cell (I), the extracellular matrix (IV), or the lysate of (III) and a pharmaceutical carrier; (9) a cell culture (V) comprising PDC in a culture medium; (10) a conditioned medium generated by the growth of the culture of (V); and (11) a kit comprising PDC and one additional component of a matrix, a hydrating agent, a cell culture substrate, a differentiation-inducing agent and cell culture media. BIOTECHNOLOGY - Preferred Cell: The cell has been isolated from a postpartum placenta or its fragment by enzymatic dissociation with at least one of a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid. Preferred Cell Population: The cell population is substantially homogeneous or is heterogeneous. The cell population further comprises at least one cell type of %bone% marrow cells, chondrocytes, chondroblasts, chondrocyte progenitor cells, osteocytes, osteoblasts, osteoclasts, %bone% lining cells, stem cells, or other pluripotent or multipotent cell. Preferred Matrix: The matrix comprises a three-dimensional scaffold. Preferred Composition: The bioactive factor is a chondrogenic or an osteogenic differentiation-inducing factor. Preferred Cell Culture: The culture medium comprises chondrogenic medium or osteogenic medium. The cell culture further comprises at least one chondrogenic or osteogenic differentiation-inducing agent. Preferred Pharmaceutical Composition: The composition comprises an amount of the cells, extracellular matrix, or lysate to treat a %bone% or cartilage condition. The pharmaceutical composition further comprises at least one other cell type of stem cells, %bone% marrow cells, chondrocytes, chondroblasts, osteocytes, osteoblasts, osteoclasts, %bone% lining cells, and other %bone% or

cartilage progenitor cells. Preferred Kit: The cell is seeded on the scaffold. The differentiation-inducing agent is an osteogenic or a chondrogenic differentiation-inducing agent. Preferred Method: Inducing differentiation of a postpartum-derived cell to a chondrogenic or an osteogenic phenotype comprises exposing the cell to one or more chondrogenic or osteogenic differentiation-inducing agents. The chondrogenic differentiation-inducing agent comprises at least one of transforming growth factor-beta3 (TGFbeta3) and growth and differentiation factor-5 (GDF-5). The osteogenic differentiation-induci ng agent comprises at least one of %bone% morphogenic protein (BMP)-2, BMP-4, and transforming growth factor-beta1. The method further comprises culturing the cell in chondrogenic medium, where the chondrogenic medium comprises Dulbecco's modified Eagle's medium, L-glutamine, sodium pyruvate, L-proline, dexamethasone, L-ascorbic acid, insulin, transferrin, selenium, and an antibiotic agent, and where the chondrogenic medium further comprises at least one of collagen and sodium hydroxide. The method further comprises culturing the cell in osteogenic medium, where the osteogenic medium comprises Dulbecco's modified Eagle's medium-low glucose, serum, beta-glycerophosphate, dexamethasone, ascorbic phosphate salt, and at least one antibiotic or antimycotic agent. The method further comprises evaluating differentiation of the cell by a pellet culture assay. The method further comprises evaluating differentiation of the cell by detecting the presence of a glycosaminoglycan or collagen, which comprises staining the cell with Safranin-O or hematoxylin/eosin. The method further comprises evaluating the differentiation by detecting an osteogenic lineage-specific marker, e.g. osteocalcin, %bone% sialoprotein, or alkaline phosphatase. The method further comprises detecting the differentiation by measuring mineralization, which comprises von Kossa staining. The postpartum-derived cells are inoculated on a matrix, where the matrix is implanted into the patient. The postpartum-derived cells are induced to differentiate to a chondrogenic or osteogenic phenotype prior to administration. ACTIVITY - Cytostatic; Osteopathic; Antiinflammatory; Antibacterial; Cerebroprotective; Neuroprotective; Antirheumatic; Antiarthritic; Vulnerary. No biological data given. MECHANISM OF ACTION - None Given. USE - Administering the cell population comprising the PDC is useful for regenerating a tissue (%bone% or cartilage) in a patient. The PDC is useful for identifying a compound that stimulates chondrogenesis or osteogenesis comprising contacting a PDC with the compound and monitoring the cell for a marker of chondrogenesis or osteogenesis. Identifying a compound that is toxic to a PDC comprises contacting the cell with the compound and monitoring survival of the cell (all claimed). The PDC, extracellular matrix, cell lysate, conditioned medium, composition and methods are useful for treating a condition (claimed), e.g. a congenital %bone% or cartilage defect, meniscal injury or defect, %bone%/spinal deformation, osteosarcoma, myeloma, %bone% dysplasia or scoliosis, osteoporosis, periodontal disease, dental %bone% loss, osteomalacia, rickets, fibrous osteitis, renal %bone% dystrophy, spinal fusion, spinal disc reconstruction or removal, Paget's disease of %bone%, rheumatoid arthritis, osteoarthritis, or traumatic or surgical injury. ADMINISTRATION - The PDC are co-administered with a bioactive factor or another cell type to a %bone% or cartilage or the cells are implanted into the patient (claimed). Administration is by intramuscular, ophthalmic, intraarterial, subcutaneous, oral, nasal, or parenteral including intravenous, intraperitoneal, intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal, and/or peri-spinal routes. No dosage given. EXAMPLE - Cells were digested in growth medium with or without 0.0001% (v/v) 2-mercaptoethanol, using the enzyme combination of C:D:H. Placenta-derived cells isolated were seeded under variety of conditions. All cells were grown in the presence of penicillin/streptomycin. The combination of C:D:H provided the best cell yield following isolation and generated cells, which expanded for many generations in culture compared to the other conditions. (61 pages)

2/7/76 (Item 7 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

0360925 DBR Accession No.: 2005-06629 PATENT

Novel isolated CD45 umbilicus-derived cell comprising cell derived from mammalian umbilical cord tissue, capable of self-renewal and expansion in culture, useful in treatment of %bone%, pancreatic, cardiac and hepatic disease or injury - involving vector-mediated gene transfer and expression in host cell for therapy and transplantation

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PATENT ASSIGNEE: ETHICON INC 2005

PATENT NUMBER: WO 200503334 PATENT DATE: 20050113 WPI ACCESSION NO.: 2005-112401 (200512)

PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627

NATIONAL APPLIC. NO.: WO 2004US20931 APPLIC. DATE: 20040625

LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated CD45 umbilicus-derived cell comprising a cell derived from mammalian umbilical cord tissue free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, where cell has a cell surface marker profile and produces CD10, CD13, CD44, CD73, CD90, platelet derived growth factor %receptor% (PDGFr)-alpha or HLA-A,B,C, is new. DETAILED DESCRIPTION - An isolated umbilicus-derived cell (I) comprises a cell derived from mammalian umbilical cord tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes, where the umbilicus-derived cell is a CD45 umbilicus-derived cell having a cell surface marker profile, where the cell produces one or more of CD10, CD13, CD44, CD73, CD90, platelet derived growth factor %receptor% (PDGFr)-alpha, or HLA-A,B,C, does not express one or more of CD31, CD34, CD117, CD141, or HLA-DR,DP,DQ, as detected by flow cytometry and does not substantially stimulate naove CD4+ T-cells and expresses PD-L2. INDEPENDENT CLAIMS are also included for: (1) a cell culture (II) comprising (I) which is free of maternal cells; (2) therapeutic cell culture (III) comprising (I); (3) deriving (M1), from umbilical tissue, an isolated cell capable of self-renewal and expansion in culture, and having the potential to differentiate into cells of other phenotypes; (4) an isolated human umbilicus-derived cell derived by (M1); (5) a therapeutic culture (IV) of human umbilicus-derived cells derived by (M1), where the culture is free of maternal cells; a conditioned culture medium (V) generated by the growth of (II) or (IV); (6) a mammalian cell culture (VI) comprising (V) and a mammalian cell in need of monocyte chemotactic protein (MCP)-1, interleukin (IL)-6, IL-8, granulocyte chemotactic protein (GCP)-2, hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), fibroblast growth factor (FGF), heparin %binding% epidermal growth factor (HB-EGF), brain derived neurotrophic factor (BDNF), thrombopoietin (TPO), or tissue inhibitor of matrix metalloprotease 1 (TIMP1); (7) a three-dimensional matrix (VII) comprising (I); (8) an implantable tissue structure comprising (VII); (9) an implantable device comprising (IV); (10) an implantable human tissue matrix comprising human umbilicus derived cell derived by (M1); (11) a human tissue comprising (I); (12) a cell lysate derived from (I); (13) a %soluble% cell fraction derived from (I); (14) a membrane-enriched cell fraction derived from (I); (15) an extracellular membrane fraction derived from (I); (16) an injectable therapeutic cell (VIII) comprising (I); and (17) an isolated postpartum-derived cell (IX). WIDER DISCLOSURE - Kits useful for the growth, isolation and use of umbilical-derived cell, are also disclosed. BIOTECHNOLOGY - Preferred Umbilical Cell: (I) can expand in the presence of oxygen 5-20%. (I) requires L-valine for growth. (I) can double sufficiently to generate yields of greater than 1014 or 1015 cells in less than 80 days in culture when seeded at 103 cells/cm2 or 5x103 cells/cm2, preferably 1017 cells in less than 65 days in culture when seeded at 5x103 cells/cm2. (I) undergoes at least 40 doublings in culture. (I) is isolated in the presence of one or more enzyme activities comprising metalloproteases, neutral proteases, or mucolytic enzymes. The enzyme activities include a collagenase, hyaluronidase, and one or more of the protease activities, dispase and thermolysin.

The enzyme activities are a collagenase from Clostridium histolyticum and dispase. (I) attaches and expands on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating with gelatin, laminin, collagen, polyornithine, polylysine, vitronectin, or fibronectin. (I) expands in the presence of 2-15% added serum, in the presence or absence of beta-mercaptoethanol, and in the presence or absence of added growth factors including epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF) or leukemia inhibitory factor (LIF). (I) maintains a normal karyotype as it is passaged. (I) produces or lacks to produce one or more cell surface markers comprising CD10, CD13, CD31, CD44, CD45, CD73, CD90, CD117, CD141, PDGFr-alpha, HLA-A,B,C, and HL-Dr, DP, DQ. The cell surface marker expression profile remains substantially unchanged with passage, culture vessel surface coating, or isolation procedure. The expression is increased relative to that of a human cell, which is fibroblast, a mesenchymal stem cell, and ileac crest %bone% marrow or placenta-derived cell. (I) produces one or both of vimentin and alpha smooth muscle actin, where the production is retained over passaging under growth conditions. Preferred Therapeutic Cell: (III) does not substantially stimulate allogeneic PBMCs. (III) lacks detectable amounts of HLA-DR, HLA-DP, HLA-DQ, CDSO, CDS6, and B7-H2, as determined by flow cytometry and further lacks detectable amounts of HLA-G and CD178. (III) produces detectable amounts of PD-L2, as determined by flow cytometry. (III) does not substantially stimulate a lymphocyte mediated response in vitro, as compared to allogeneic controls in a mixed lymphocyte reaction. (III) further comprises one or more of a carrier, another cell culture, an antiapoptotic compound, antithrombogenic compound, anti-inflammatory compound, immunosuppressive compound, immunomodulatory compound, angiogenic factor and neurotrophic factor. Preferred Method: (M1) involves obtaining umbilical tissue, removing substantially all of blood to yield a substantially blood-free umbilical tissue, dissociating the tissue by mechanical or enzymatic treatment, or both, resuspending the tissue in a culture medium, and providing growth conditions which allow for the growth of an umbilicus-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into cells of other phenotypes. (M1) further involves selecting adherent cells after 10-100 hours in culture. The derived cell is capable of to expansion in the absence of added growth factors in medium with 2-15% added serum. The umbilical tissue is obtained after normal or surgically-assisted child birth from a full-term or pre-term pregnancy. The dissociation step comprises the use of one or more enzyme activities chosen from metalloprotease, hyaluronidase, and neutral protease, preferably collagenase and dispase. The enzyme activities further include hyaluronidase. The dissociating step comprises incubating at 370C for one or more hours, preferably 2 hours. The removing step comprises removal of free or clotted blood by one or more of washing, suctioning, blotting, centrifugal separation, or enzymatic removal. The dissociating step is accomplished aseptically and comprises one or more of mincing, blending, homogenizing or grinding. Preferred Mammalian Culture: (VI) comprises the umbilicus-derived cells and another mammalian cell of any phenotype, preferably a human cell line in addition to the umbilicus-derived cell. Preferred Matrix: (VII) comprises a biocompatible or bioabsorbable polymer. (VII) comprises Vicryl matrix, PCL/PGA copolymer, or self assembling %peptides%. Preferred Injectable Cell: (VIII) is treated to inactivate tissue factor. The treatment is with an anti-tissue factor antibody. Preferred Postpartum-Derived Cell: (IX) comprises an L-valine-requiring cell derived from human postpartum tissue substantially free of blood, the cell capable of self-renewal and expansion in culture and having the potential to differentiate into a cell of cardiomyocyte phenotypes, the cell capable of growth in an atmosphere containing oxygen 5-20%, where the cell comprises any one of the characteristics such as potential for at least about 40 doublings in culture; attachment and expansion on a coated or uncoated tissue culture vessel, where a coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; production of a tissue factor, vimentin, or alpha-smooth muscle actin; production of a CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 or HLA-A,B,C; lack of production of a CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD 78, B7-H2, HLA-G, or HLA-DR,DP,DQ, as detected by flow cytometry; expression of an interleukin 8, reticulon 1, chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha), chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2), chemokine (C-X-C motif) ligand 3, or tumor necrosis factor, alpha- induced protein 3; expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for any one of short stature homeobox 2, heat shock 27 kDa protein 2, chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1), elastin (supravalvular aortic stenosis, Williams-Beuren syndrome), Homo sapiens mRNA, cDNA DKFZp586M2022 (from clone DKFZp586M2022), mesenchyme homeobox 2 (growth arrest- specific homeobox), sine oculis homeobox homolog 1 Drosophilacrystallin, alpha B, dishevelled associated activator of morphogenesis 2, DKFZp586B2420 protein, similar to neuralin 1, tetranectin (plasminogen %binding% protein), src homology three (SH3) and cysteine rich domain, B-cell translocation gene 1, anti-proliferative, cholesterol 25-hydroxylase, runt- related transcription factor 3, hypothetical protein FLJ23191, %interleukin% %11% %receptor% , alpha, procollagen C-endopeptidase enhancer, frizzled homolog 7 Drosophilahypothetical gene BC008967, collagen, type VII, alpha 1, tenascin C (hexabrachion), iroquois homeobox protein 5, hephaestin, integrin, beta 8, synaptic vesicle glycoprotein 2, Homo sapiens cDNA FLJ12280 fis, clone MAMMA 1001744, cytokine %receptor% -like factor 1, potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4, integrin, alpha 7, DKFZP586L151 protein, transcriptional co-activator with PDZ- %binding% motif (TAZ), sine oculis homeobox homolog 2 DrosophilaKIAA1034 protein, early growth response 3, distal-less homeobox 5, hypothetical protein FLJ20373, aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II), biglycan, fibronectin 1, proenkephalin, integrin, beta-like 1 (with epidermal growth factor (EGF))-like repeat domains), Homo sapiens mRNA full-length insert cDNA clone EUROIMAGE 1968422, EphA3, KIAA0367 protein, natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C), hypothetical protein FLJ14054, Homo sapiens mRNA, cDNA DKFZp564B222 (from clone DKFZp564B222), vesicle-associated membrane protein 5 (myobrevin), EGF-containing fibulin-like extracellular matrix protein 1, BCL2/adenovirus E1B 19 kDa interacting protein 3-like, AE %binding% protein 1, cytochrome c oxidase subunit VIIIa %polypeptide% 1 (muscle), neuroblastoma, suppression of tumorigenicity 1, insulin-like growth factor %binding% protein 2.36 kDa; secretion of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIP1a, regulated on activation, normal T-cell expressed and secreted (RANTES), or TIMP1; and lack of secretion of TGF-beta2, angiopoietin 2 (ANG2), PDGFbb, MIP1beta, 1309, MDC, and vascular endothelial growth factor (VEGF), as detected by enzyme linked immunosorbent assay (ELISA). ACTIVITY - Cardiant; Nephrotropic; Osteopathic; Hepatotropic; Ophthalmological. The ophthalmological activity of the umbilical derived cells was determined in vivo. Cultures of human adult umbilical and fibroblast cells (passage 10) were expanded for 1 passage. Cells were delivered into the dorso-temporal subretinal space of anesthetized 3 week-old dystrophic-pigmented RCS rats (total N=10/cell type). Cells were injected unilaterally into the right eye, while the left eye was injected with carrier medium alone. After cell injections were performed, animals were injected with dexamethasone (2 mg/kg) for 10 days post transplantation. For the duration of the study, animals were maintained on oral cyclosporin A. Animals were sacrificed at 60 or 90 days postoperatively and observed. The observation results indicated that visual responsiveness was improved in umbilicus-derived cell transplanted animals with evidence for photoreceptor rescue. MECHANISM OF ACTION - Angiogenesis promoter. USE - (I) isolated from human umbilicus is useful for preparing therapeutic cell culture (claimed). (I) is useful for therapeutic uses such as angiogeneic applications, neuronal applications, soft tissue applications, ocular applications and applications where the cells are useful in treatment of heart, kidney, %bone%, cartilage, pancreas, liver and other tissues alone or in combination with other therapeutic agents. (I) is useful in promoting angiogenesis. (III) is useful in the treatment of %bone%

disease or injury, pancreatic disease, kidney disease, cardiac disease or injury, and hepatic disease or injury. (153 pages)

2/7/77 (Item 8 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0359576 DBR Accession No.: 2005-05280 PATENT
New postpartum-derived cell that self-renews and expands in culture, and provides trophic support to a soft tissue cell, useful for treating a soft tissue condition, such as hernia, ulcer, burn, surgical wound or vascular disorders - a pharmaceutical composition comprising a cell population including postpartum-derived cell, stem cell, adipocyte and keratinocyte useful for disease cell therapy
AUTHOR: HARMON A M; HARRIS I R; KIHM A J; MISTRY S; MESSINA D J; SEYDA A; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200501079 PATENT DATE: 20050106 WPI ACCESSION NO.: 2005-075563 (200508)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20956 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A postpartum-derived cell (PPDC) comprising a cell derived from human postpartum tissue substantially free of blood, where the PPDC self-renews and expands in culture, provides trophic support to a soft tissue cell, and grows in 5-20% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a cell population comprising the postpartum-derived cell; (2) a cell lysate prepared from the cell population; (3) a %soluble% cell fraction prepared from the cell lysate; (4) an extracellular matrix of the cell population; (5) a composition comprising the cell population, and one or more bioactive factors; (6) a pharmaceutical composition comprising the cell, extracellular matrix or cell lysate and a carrier; (7) a cell culture comprising at least one cell in a culture medium; (8) a conditioned medium of the cell population; (9) providing trophic support to a soft tissue cell by exposing the soft tissue cell to the postpartum-derived cell or the conditioned medium; (10) inducing angiogenesis comprising exposing a population of soft tissue cells to the cell or conditioned medium; (11) a matrix comprising the cell population; (12) treating a patient in need of angiogenic factors comprising administering to the patient the cell population, conditioned medium, extracellular matrix or cell lysate; (13) treating a soft tissue condition in a patient comprising administering to the patient the cell population, conditioned medium, matrix, extracellular matrix or cell lysate; (14) a kit comprising at least one of the cell and at least one additional component of a matrix, a hydrating agent, a cell culture substrate, a bioactive factor, a second cell type, a differentiation-inducing agent, and cell culture media; (15) producing a vascular network comprising exposing a population of soft tissue cells to the cell population, cell lysate, extracellular matrix, or conditioned medium; (16) a vascular network produced by the method; and (17) treating a condition in a patient comprising administering the vascular network to the patient. BIOTECHNOLOGY - Preferred Cell: The postpartum-derived cell further comprises at least one of the following characteristics: (a) production of at least one of granulocyte chemotactic protein 2 (GCP-2), reticulon 1, tissue factor, vimentin, and alpha-smooth muscle actin; (b) lack of production of at least one of GRO-alpha or oxidized low density lipoprotein %receptor%, as detected by flow cytometry; (c) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and HLA-A5B5C; (d) lack of production of at least one of CD31 CD34, CD45, CDSO5 CD86, CD117, CD141, CD178, B7-H2, HLA-G5 and HLA-DR5DP5DQ, as detected by flow cytometry; (e) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for at least one of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3 or expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for at least one of C-type lectin superfamily member A2, Wilms tumor 1, aldehyde dehydrogenase 1 family member AZ5 renin, oxidized low density lipoprotein %receptor% 1, protein kinase C zeta, clone IMAGE:4179671, hypothetical protein DKFZp564F013, downregulated in ovarian cancer 1, and clone DKFZp547KI 113; (f) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin; cDNADKFZp586M2022 (from clone DKFZpS86M2022); mesenchyme homeobox 2; sine oculis homeobox homolog 1; crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin; src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7; hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C; iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; cDNA FLJ12280 fis, clone MAMMAI001744; cytokine %receptor%-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2; KIAAI034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); cDNA clone EUROIMAGE 1968422; EphAS; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJI4054; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5; EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus EIB 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36kDa; (g) secretion of at least one of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIPIa, RANTES, and TIMP1; (h) lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MIP 1beta, I309, MDC, and VEGF, as detected by ELISA; and (i) the ability to undergo at least 40 population doublings in culture. The postpartum-derived cell has been isolated from a post-partum placenta or its fragment by enzymatic dissociation with at least one of a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid. The cell is induced to differentiate to a soft tissue phenotype. The soft tissue cell is a cell of cartilage tissue, meniscal tissue, ligament tissue, tendon tissue, intervertebral disc tissue, periodontal tissue, skin tissue, vascular tissue, muscle tissue, fascia tissue, periosteal tissue, ocular tissue, pericardial tissue, lung tissue, synovial tissue, nerve tissue, kidney tissue, %bone% marrow, urogenital tissue, intestinal tissue, liver tissue, pancreas tissue, spleen tissue, or adipose tissue. Preferred Population: The cell population is substantially homogeneous or heterogeneous. The cell population further comprises at least one cell type of %bone% marrow cells, adipocytes, stem cells, keratinocytes, vascular endothelial cells, myoblasts, myocytes, stromal cells, and other soft tissue progenitor cells. Preferred Composition: The composition further comprise a bioactive factor that is at least one of a differentiation-inducing factor, an anti-apoptotic agent, an anti-inflammatory agent, an immunosuppressive/immunomodulatory agent, an anti-proliferative agent, a corticosteroid, an antibody, an anti-thrombogenic agent, an anti-oxidant, and scar inhibitory factor. The pharmaceutical composition comprises an effective amount of the cells, extracellular matrix or lysate to treat a soft tissue condition. The pharmaceutical composition further comprises at least one other cell type of stem cells, epithelial cells, dermal fibroblasts, melanocytes, keratinocytes, and other epithelial progenitor cells. The pharmaceutical composition further comprises at least one other cell

type of stem cells, myocytes, myoblasts, and muscle cells. The pharmaceutical composition further comprises at least one cell type of stem cells, epithelial cells, endothelial cells, and stromal cells. Preferred Method: In providing trophic support to a soft tissue cell, the soft tissue cell is a stem cell, a myocyte, a myoblast, a keratinocyte, a melanocyte, a dermal fibroblast, a %bone% marrow cell, an adipocyte, an epithelial cell, an endothelial cell, or a stromal cell. The soft tissue cell comprises at least one of aortic endothelial cells, coronary artery endothelial cells, pulmonary artery endothelial cells, iliac artery endothelial cells, microvascular endothelial cells, umbilical artery endothelial cells, umbilical vein endothelial cells, and endothelial progenitors. The step of exposing stimulates angiogenesis by the endothelial cells. Inducing angiogenesis is in vitro or in vivo. In treating a soft tissue condition in a patient, the treatment comprises at least one of soft tissue repair, reconstruction, bulking, cosmetic treatment, therapeutic treatment, tissue augmentation, and tissue sealing. The step of administering comprises implanting or injecting the cell population. In treating a condition in a patient, the vascular network is administered by transplantation to the patient. The condition is a soft tissue condition, e.g. a vascular condition, such as vascular disease or injury or improper vascular development. In producing a vascular network, the population of soft tissue cells comprises at least one soft tissue cell of an aortic endothelial cell, coronary artery endothelial cell, pulmonary artery endothelial cell, iliac artery endothelial cell, microvascular endothelial cell, umbilical artery endothelial cell, and umbilical vein endothelial cell. The method is in vitro or in vitro. Preferred Matrix: The matrix comprises a three-dimensional scaffold. The scaffold is flat, tubular or multilayered. ACTIVITY - Gastrointestinal-Gen; Vulnerary; Muscular-Gen; Vasotropic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The cell, cell population, compositions and vascular network are useful for treating soft tissue condition is a congenital defect, a hernia, damage to the pelvic floor, tear or rupture of a tendon or ligament, a scar, a burn, an ulcer, a surgical wound, a traumatic wound, a vascular disease, or a muscle disease (claimed). ADMINISTRATION - Administration is by implanting or injecting the cell population, or transplanting the vascular network to the patient (claimed). No dosage is given. EXAMPLE - Cells were isolated from cord blood samples. Samples of umbilical cord blood were mixed with lysis buffer. Cells were lysed at a ration of 1:20 cord blood to lysis buffer. The resulting cell suspension was vortexed for 5 seconds, and incubated for 2 minutes at ambient temperature. The lysate was centrifuged. The cell pellet was resuspended in complete minimal essential medium containing 10 percent fetal bovine serum, 4 millimolar glutamine, 100 units penicillin per 100 millimeters and 100 micrograms streptomycin per 100 millimeters. The resuspended cells were centrifuged, the supernatant was aspirated, and the cell pellet was washed in complete medium. Cells were seeded directly into T75 flasks, T75 laminin-coated flasks, or T175 fibronectin-coated flasks. (135 pages)

2/7/78 (Item 9 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0359575 DBR Accession No.: 2005-05279 PATENT
New isolated postpartum-derived cell having the potential to differentiate into a cell of a neural phenotype, useful for treating a neurodegenerative condition, e.g. Alzheimer's disease, Parkinson's disease, brain trauma - a pharmaceutical composition comprising human postpartum cell useful for disease cell therapy and tissue engineering application
AUTHOR: MESSINA D J; MISTRY S; HARMON A M; HARRIS I R; KIHM A J; SEYDA A; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200501078 PATENT DATE: 20050106 WPI ACCESSION NO.: 2005-075562 (200508)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20823 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated postpartum-derived cell comprising a cell derived from human placental or umbilical cord tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of a neural phenotype, and where the cell requires L-valine for growth and is capable of growth in at least about 5% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a cell population comprising the postpartum-derived cell; (2) a cell lysate prepared from the cell population; (3) a %soluble% cell fraction prepared from the cell lysate; (4) an extracellular matrix prepared from the cell population; (5) treating a patient having a neurodegenerative condition; (6) a pharmaceutical composition for treating a patient having a neurodegenerative condition, comprising a carrier and the postpartum-derived cells in an effective to treat the neurodegenerative condition; (7) a kit for treating a patient having a neurodegenerative condition, the kit comprising a carrier, a population of postpartum-derived cells and instructions for using the kit in a method of treating the patient; (8) increasing the survival, growth or activity of neural lineage cells comprising co-culturing the neural lineage cells with the postpartum-derived cells under conditions effective to increase the survival, growth or activity of the neural lineage cells; and (9) a kit for increasing the survival, growth or activity of neural lineage cells comprising the postpartum-derived cells and instructions for co-culturing the neural lineage cells with the postpartum-derived cells under conditions effective to increase the survival, growth or activity of the neural lineage cells. BIOTECHNOLOGY - Preferred Cell: The isolated postpartum-derived cell further comprises at least one of the following characteristics: (a) potential for at least about 40 doublings in culture; (b) attachment and expansion on a coated or uncoated tissue culture vessel, where the coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; (c) production of at least one of tissue factor, vimentin, and alpha-smooth muscle actin; (d) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and HLA-A,B,C; (e) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR,DP,DQ, as detected by flow cytometry; (f) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for at least one of a gene encoding: interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; tumor necrosis factor, alpha-induced protein 3; C-type lectin superfamily member 2; Wilms tumor 1; aldehyde dehydrogenase 1 family member A2; renin; oxidized low density lipoprotein %receptor% 1; Homo sapiens clone IMAGE:4179671; protein kinase C zeta; hypothetical protein DKFZp564F013; downregulated in ovarian cancer 1; and Homo sapiens gene from clone DKFZp547kl 113; (g) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of a gene encoding: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); Homo sapiens mRNA; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeo box 2 (growth arrest-specific homeo box); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; cholesterol 25-hydroxylase; runt-related transcription factor 3; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36kDa; Homo sapiens cDNA F1J12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin,

beta 7; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; early growth response 3; distal-less homeo box 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type H); biglycan; transcriptional co-activator with PDZ-%binding% motif (TAZ); fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; Homo sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); similar to neuralin 1; B cell translocation gene 1; hypothetical protein FLJ23191; and DKFZp586L151; (h) secretion of at least one of MCP-1, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIP1alpha, RANTES, and TEVIP1; and (i) lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MTPIb, 1309, MDC, and VEGF, as detected by ELISA. The cell is isolated in the presence of one or more enzyme activities comprising metalloprotease activity, mucolytic activity and neutral protease activity. The cell comprises a normal karyotype. The cell comprises each of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, and HLA-A,B,C and does not comprise any of CD31, CD34, CD45, CD117, CD141, or HLA-DR,DP,DQ, as detected by flow cytometry. Preferred Cell Population: The cell population is a substantially homogeneous population of the postpartum-derived cells. The population comprises a clonal cell line of postpartum-derived cells. The cell population is a heterogeneous population comprising the postpartum-derived cells and at least one other cell type. The at least one other cell type is an astrocyte, oligodendrocyte, neuron, neural progenitor, neural stem cell or other multipotent or pluripotent stem cell. The cell population is cultured in contact with one or more factors that stimulate stem cell differentiation toward a neural or epithelial lineage. Preferred Method: Treating a patient having a neurodegenerative condition comprises administering to the patient postpartum-derived cells in an amount effective to treat the neurodegenerative condition. The neurodegenerative condition is an acute neurodegenerative condition, such as brain trauma, spinal cord trauma or peripheral nerve trauma. The neurodegenerative condition is a chronic or progressive neurodegenerative condition, such as Parkinson's disease, Alzheimer's disease, Huntingdon's disease, amyotrophic lateral sclerosis, tumor, multiple sclerosis or chronic peripheral nerve injury. The cells are induced in vitro to differentiate into a neural lineage cells prior to administration. The cells are genetically engineered to produce a gene product that promotes treatment of the neurodegenerative condition. The cells are administered with at least one other cell type. The other cell type is an astrocyte, oligodendrocyte, neuron, neural progenitor, neural stem cell or other multipotent or pluripotent stem cell. The at least one other cell type is administered simultaneously with, or before, or after, the postpartum-derived cells. The cells are administered with at least one other agent. The at least one other agent is administered simultaneously with, or before, or after, the postpartum-derived cells. The cells are administered at a pre-determined site in the central or peripheral nervous system of the patient. The cells are administered by injection or infusion. The cells are administered encapsulated within an implantable device. The cells are administered by implantation of a matrix or scaffold containing the cells. The treatment method further comprises administering to the patient a preparation made from the postpartum-derived cells, where the preparation comprises a cell lysate of the postpartum-derived cells, an extracellular matrix of the postpartum-derived cells, or a conditioned medium in which the postpartum-derived cells were grown. Preferred Composition: The pharmaceutical composition further comprises at least one other agent. The cells are contained within a matrix or scaffold. The pharmaceutical composition alternatively comprises a carrier and a preparation made from the postpartum-derived cells, where the preparation comprises a cell lysate of the postpartum-derived cells, an extracellular matrix of the postpartum-derived cells or a conditioned medium in which the postpartum-derived cells were grown. Preferred Kit: The kit further comprises at least one reagent and instructions for culturing the postpartum-derived cells. It further comprises a population of at least one other cell type, or at least one other agent for treating a neurodegenerative condition. The kit alternatively comprises a carrier, the preparation cited above, and instructions for using the kit components for treatment of the neurodegenerative condition. ACTIVITY - Neuroprotective; Nootropic; Cerebroprotective; Antiparkinsonian; Cytostatic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The cell, cell population, compositions and methods are useful for treating neurodegenerative condition, which is an acute neurodegenerative condition, such as brain trauma, spinal cord trauma or peripheral nerve trauma. The neurodegenerative condition is a chronic or progressive neurodegenerative condition, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, tumor, multiple sclerosis or chronic peripheral nerve injury (all claimed). ADMINISTRATION - The cells are administered by injection or infusion (claimed). No dosage is given. EXAMPLE - Cells were isolated from cord blood samples. Samples of umbilical cord blood were mixed with lysis buffer. Cells were lysed at a ration of 1:20 cord blood to lysis buffer. The resulting cell suspension was vortexed for 5 seconds, and incubated for 2 minutes at ambient temperature. The lysate was centrifuged. The cell pellet was resuspended in complete minimal essential medium containing 10 percent fetal bovine serum, 4 millimolar glutamine, 100 units penicillin per 100 millimeters and 100 micrograms streptomycin per 100 millimeters. The resuspended cells were centrifuged, the supernatant was aspirated, and the cell pellet was washed in complete medium. Cells were seeded directly into T75 flasks, T75 laminin-coated flasks, or T175 fibronectin-coated flasks. (117 pages)

2/7/79 (Item 10 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0359574 DBR Accession No.: 2005-05278 PATENT
New isolated postpartum-derived cell that is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of a neural phenotype, useful for treating glaucoma, diabetic retinopathy, retinitis - a pharmaceutical composition comprising a postpartum cell, stem cell and progenitor cell useful for disease cell therapy
AUTHOR: MISTRY S; MESSINA D J; HARRIS I R; HARMON A M; KIHM A J; SEYDA A; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200501077 PATENT DATE: 20050106 WPI ACCESSION NO.: 2005-075561 (200508)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20822 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated postpartum-derived cell comprising a cell derived from human placental or umbilical cord tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and has the potential to differentiate into a cell of a neural phenotype, requires L-valine for growth and is capable of growth in at least about 5% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a cell population comprising the postpartum-derived cell; (2) a cell lysate prepared from the cell population; (3) a %soluble% cell fraction prepared from the cell lysate; (4) an extracellular matrix prepared from the cell population; (5) treating a patient having an ocular degenerative condition; (6) a pharmaceutical composition for treating a patient having an ocular degenerative condition, comprising a carrier and multipotent or pluripotent cells isolated from a postpartum placenta or umbilical cord in an amount effective to treat the ocular degenerative condition; (7) a kit for treating a patient having an ocular degenerative condition, the kit comprising a carrier, a population of multipotent or pluripotent cells isolated from postpartum placenta or umbilicus, and instructions for using the kit in a method

of treating the patient; (8) increasing the survival, growth or activity of cells for transplantation to treat an ocular degenerative disorder; and (9) a kit for increasing the survival, growth or activity of cells for transplantation to treat an ocular degenerative disorder, comprising cultured cells derived from postpartum placental or umbilical tissue and instructions for co-culturing the cells for transplantation with the postpartum cells under conditions effective to increase the survival, growth or activity of the cells for transplantation. BIOTECHNOLOGY - Preferred Cell: The isolated postpartum-derived cell further comprises at least one of the following characteristics: (a) a potential for at least about 40 doublings in culture; (b) attachment and expansion on a coated or uncoated tissue culture vessel, where the coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; (c) production of at least one of tissue factor, vimentin, and alpha-smooth muscle actin; (d) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2andHLA-A,B,C; (e) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR,DP,DQ, as detected by flow cytometry; (f) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is increased for at least one of a gene encoding: interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; tumor necrosis factor, alpha-induced protein 3; C-type lectin superfamily member 2; Wilms tumor 1; aldehyde dehydrogenase 1 family member A2; renin; oxidized low density lipoprotein %receptor% 1; Homo sapiens clone IMAGE:4179671; protein kinase C zeta; hypothetical protein DKFZp564F013; downregulated in ovarian cancer 1; and Homo sapiens gene from clone DKFZp547k1 113; (g) expression of a gene, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of a gene encoding: short stature homeobox 2; heat shock 27 kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); Homo sapiens mRNA; cDNA DKFZpS86M2022 (from clone DKFZp586M2022); mesenchyme homeo box 2 (growth arrest-specific homeo box); sine oculis homeobox homolog 1 (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; cholesterol 25-hydroxylase; runt-related transcription factor 3; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36kDa; Homo sapiens cDNA FLJ12280 fis, clone MAMMA1001744; cytokine %receptor% -like factor 1; potassium intermediate or small conductance calcium-activated channel, subfamily N, member 4; integrin, beta 7; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; early growth response 3; distal-less homeo box 5; hypothetical protein FU20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; transcriptional co-activator with PDZ-%binding% motif (TAZ); fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); Homo sapiens mRNA full-length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; Homo sapiens mRNA; cDNA DKFZp564B222 (from clone DKFZp564B222); BCL2 adenovirus EIB 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); similar to neuralin 1; B cell translocation gene 1; hypothetical protein FLJ23191; and DKFZp586L151; and (h) secretion of at least one of MCP-I, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIPIa, RANTES, and TIMP1; and (i) lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MIPIb, 1309, MDC, and VEGF, as detected by ELISA. The cell is isolated in the presence of one or more enzyme activities comprising metalloprotease activity, mucolytic activity and neutral protease activity. The postpartum-derived cell comprises a normal karyotype. The cell comprises each of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, and HLA-A,B,C and does not comprise any of CD31, CD34, CD45, CD117, CD141, or HLA-DR,DP,DQ, as detected by flow cytometry. Preferred Population: The cell population is a substantially homogeneous population of the postpartum-derived cells. The population comprises a clonal cell line of postpartum-derived cells. This population can be a heterogeneous population comprising the postpartum-derived cells and at least one other cell type. The at least one other cell type is an astrocyte, oligodendrocyte, neuron, neural progenitor, neural stem cell, retinal epithelial stem cell, corneal epithelial stem cell or other multipotent or pluripotent stem cell. The cell population is cultured in contact with one or more factors that stimulate stem cell differentiation toward a neural or epithelial lineage. Preferred Method: Treating a patient having an ocular degenerative condition comprises administering to the patient multipotent or pluripotent cells isolated from a postpartum placenta or umbilical cord, in an amount effective to treat the ocular degenerative condition. The ocular degenerative condition is an acute ocular degenerative condition, such as brain trauma, optic nerve trauma or ocular lesion. The ocular degenerative condition is a chronic or progressive degenerative condition, such as macular degeneration, retinitis pigmentosa, diabetic retinopathy, glaucoma or limbal epithelial cell deficiency. The multipotent or pluripotent cells are isolated postpartum-derived cells derived from human placental or umbilical cord tissue substantially free of blood, where the cells are capable of self-renewal and expansion in culture and have the potential to differentiate into cells of at least a neural phenotype; and where the cells require L-valine for growth and can grow in at least about 5% oxygen. The cells are induced in vitro to differentiate into a neural or epithelial lineage cells prior to administration. The cells are administered. with at least one other cell type. The other cell type is an astrocyte, oligodendrocyte, neuron, neural progenitor, neural stem cell, retinal epithelial stem cell, corneal epithelial stem cell, or other multipotent or pluripotent stem cell. The at least one other cell type is administered simultaneously with, or before, or after, the postpartum-derived cells. The cells are administered with at least one other agent. The at least one other agent is administered simultaneously with, or before, or after, the cells. The cells are administered to the surface of an eye, interior of an eye, or through a cannula or from a device implanted in the patient's body within or in proximity to the eye. The cells are administered by implantation of a matrix or scaffold containing the cells. The preparation comprises a cell lysate of the cells, or a conditioned medium in which the cells were grown or an extracellular matrix of the cells. Increasing the survival, growth or activity of cells for transplantation to treat an ocular degenerative disorder comprises co-culturing the cells for transplantation with cultured cells derived from postpartum placental or umbilical tissue, under conditions effective to increase the survival, growth or activity of the cells for transplantation. Preferred Composition: The pharmaceutical composition comprises at least one other agent. The other agent is a drug for treating the ocular degenerative disorder. The composition is formulated for administration to the surface or interior of an eye. The composition is formulated as a matrix or scaffold containing the cells. Preferred Kit: The kit for the treatment method further comprises at least one reagent and instructions for culturing the cells; a population of at least one other cell type; and at least one other agent for treating an ocular degenerative condition. ACTIVITY - Ophthalmological. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The cell, composition, population of cells and methods are useful for treating an ocular degenerative condition, e.g. an acute ocular degenerative condition, such as brain trauma, optic nerve trauma or ocular lesion. The ocular degenerative condition is a chronic or progressive degenerative condition, such as macular degeneration, retinitis pigmentosa, diabetic retinopathy, glaucoma or limbal epithelial cell deficiency (all claimed). ADMINISTRATION - The cells are administered to the surface of an eye, interior of an eye, or through a cannula or from a device

implanted in the patient's body within or in proximity to the eye (claimed). No dosage is given. EXAMPLE - Cells were isolated from cord blood samples. Samples of umbilical cord blood were mixed with lysis buffer. Cells were lysed at a ration of 1:20 cord blood to lysis buffer. The resulting cell suspension was vortexed for 5 seconds, and incubated for 2 minutes at ambient temperature. The lysate was centrifuged. The cell pellet was resuspended in complete minimal essential medium containing 10 percent fetal bovine serum, 4 millimolar glutamine, 100 units penicillin per 100 millimeters and 100 micrograms streptomycin per 100 millimeters. The resuspended cells were centrifuged, the supernatant was aspirated, and the cell pellet was washed in complete medium. Cells were seeded directly into T75 flasks, T75 laminin-coated flasks, or T175 fibronectin-coated flasks. (123 pages)

2/7/80 (Item 11 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0359573 DBR Accession No.: 2005-05277 PATENT
New placenta-derived cell that self-renews and expands in culture, and that is multipotent, useful for treating patients requiring the repair or replacement of a tissue or organ, or for providing cosmetic function - human cell culture and expansion for use in tissue repair and tissue engineering
AUTHOR: KIHM A J; HARRIS I R; MISTRY S; HARMON A M; MESSINA D J; SEYDA A; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200501076 PATENT DATE: 20050106 WPI ACCESSION NO.: 2005-075560 (200508)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20816 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A placenta-derived cell comprising a cell derived from human postpartum placenta tissue substantially free of blood, where the cell self-renews and expands in culture, is multipotent, requires L-valine for growth, or grows in 5-20% oxygen, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a homogeneous cell population comprising the cell; (2) a heterogeneous cell population comprising the cell; (3) a cell culture comprising at least one of the cell; (4) an extracellular matrix produced by the cell; (5) a cell lysate of the cell; (6) a matrix comprising the cell; (7) isolating a placenta-derived cell from a post-partum human placenta or its fragment by dissociating the cell from the placenta or its fragment with a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid; (8) a matrix comprising the extracellular matrix; (9) producing a population of placenta-derived cells by expanding the cell in culture; (10) a conditioned culture medium generated by the growth of the culture; (11) a cell culture comprising the conditioned medium and a mammalian cell in need of at least one of interleukin 8 (EL8), tissue factor, hepatocyte growth factor (HGF), monocyte chemotactic protein 1 (MCP-1), keratinocyte growth factor (KGF), tissue inhibitor of matrix metalloproteinase 1 (TIMP1), thrombopoietin (TPO), heparin-%binding% epidermal growth factor (HB-EGF), stromal-derived factor 1-alpha (SDF-1alpha), brain-derived neurotrophic factor (BDNF), interleukin-6 (EL-6), granulocyte chemotactic protein-2 (GCP-2), macrophage inflammatory protein 1-alpha (MIP1alpha), monocyte chemoattractant-1 (MCP-I), Rantes (regulated on activation, normal T cell expressed and secreted), thymus and activation-regulated chemokine (TARC), and Eotaxin; and (12) a kit comprising that at least one cell and at least one additional component of a scaffold, a hydrating agent, a cell culture substrate, and cell culture media. BIOTECHNOLOGY - Preferred Cell: The placental-derived cell further comprises at least one of the following characteristics: (a) production of at least one of tissue factor, vimentin, granulocyte chemotactic protein-2 (GCP-2), and alpha-smooth muscle actin; (b) lack of production of at least one of GRO-alpha and oxidized low density lipoprotein receptor, as detected by flow cytometry; (c) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2andHLA-A,B,C; (d) lack of production of at least one of CD31, and clone DKFZp547K1113; (e) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin; cDNA DKFZp586M2022 (from clone DKFZp586M2022); mesenchyme homeobox 2; sine oculis homeobox homolog 1; crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin; src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; runt-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% receptor, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7; hypothetical gene BC008967; collagen, type VD1, alpha 1; tenascin C; iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; cDNA FLJ12280 fis, clone MAMMA1001744; cytokine receptor-like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2; KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); cDNA clone EUROEVIAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% receptor C/guanylate cyclase C (atrionatriuretic %peptide% receptor C); hypothetical protein FLJ14054; cDNA DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5; EGF-containing fibulin like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit VIIa %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; and insulin-like growth factor %binding% protein 2, 36kDa; (f) secretion of at least one of monocyte chemotactic protein 1 (MCP-1), interleukin- 6 (IL-6), stromal-derived factor 1 alpha (SDF-1alpha), interleukin 8 (IL8), granulocyte chemotactic protein-2 (GCP-2), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), heparin-%binding% epidermal growth factor (HB-EGF), brain-derived neurotrophic factor (BDNF), tissue inhibitor of matrix metalloproteinase 1 (TIMP1), thrombopoietin (TPO), macrophage inflammatory protein 1alpha(MIP1alpha), Rantes (regulated on activation, normal T cell expressed and secreted), thymus and activation-regulated chemokine (TARC), and Eotaxin; (g) lack of secretion of at least one of fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), angiopoietin 2 (ANG2), platelet derived growth factor (PDGF-bb), transforming growth factor beta2 (TGFbeta2), macrophage inflammatory protein1 beta (MIP1b), 1309, and macrophage-derived chemokine (MDC), as detected by ELISA; and (h) the ability to undergo at least 40 population doublings in culture. The cell has been isolated from a post-partum placenta or its fragment by enzymatic dissociation. The cell is isolated by enzymatic dissociation with a matrix metalloprotease, a neutral protease, and a mucolytic enzyme that digests hyaluronic acid. The matrix metalloprotease is collagenase. The neutral protease is dispase. The mucolytic enzyme is hyaluronidase. The cell is passaged 0-25 times. The cell is of a neonatal or maternal lineage. The cell expands in culture medium comprising Dulbecco's modified Eagle's medium (DMEM)-low glucose, DMEM-high glucose, mesenchymal stem cell growth medium, RPMII 640, CELL-GRO FREE, advanced DMEM (Gibco), DMEM/MCDB201 (Sigma), Ham's F10 medium, Ham's F12 medium, DMEM/F12, Iscove's modified Dulbecco's medium, or Eagle's basal medium. The culture medium comprises 2%-15% (v/v) serum. The culture medium comprises betamercaptoethanol. The culture medium comprises at least one antibiotic agent. The cell expands in the following culture media in order of growth: Growth medium greater than MSCGM greater than Iscove's + 10% serum, which is equal to DMEM-high glucose + 10% serum; Ham's F12 + 10% serum; and RPMI1640 + 10% serum. The cell grows in protein-free, or serum-free culture medium. The cell cannot grow in the absence of L-valine. The cell grows in the presence of at least one of fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, and epidermal growth factor. The cell grows

on an uncoated surface. The cell grows on a surface coated with collagen, fibronectin, vitronectin, ornithine, laminin, or extracellular membrane protein. The characteristics of the cell are stable with passage of the cell. The cell is genetically engineered to produce a protein of interest. Preferred Population: The heterogeneous cell population comprises at least 10% of the cells. This cell population further comprises at least one of a stem cell or progenitor cell having the ability to differentiate into a mesodermal, ectodermal, or endodermal phenotype. The cell population further comprises at least one growth factor of platelet derived growth factor-bb, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or leukemia inhibitory factor. Preferred Culture: The cell culture further comprises at least one growth factor of platelet derived growth factor-bb, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or leukemia inhibitory factor. The cell culture can undergo at least 40 population doublings in culture. The mammalian cell is a stem cell or a progenitor cell. Preferred Matrix: The matrix is a three-dimensional scaffold. The matrix comprises VICRYL nonwoven scaffold, 35/65 PCUPGA foam, an in situ polymerizable gel, or a self-assembling %peptide% hydrogel. Preferred Method: In isolating a placenta-derived cell from a post-partum human placenta or its fragment, the matrix metalloprotease comprises collagenase. The neutral protease comprises dispase. The mucolytic enzyme comprises hyaluronidase. The method further comprises mechanically dissociating the placenta or its fragment prior to the dissociating step. The method further comprises growing the cell in culture medium. The culture medium comprises RPMI1640, Ham's F10 medium, Ham's F12 medium, Mesenchymal Stem Cell Growth Medium, Iscove's modified Dulbecco's medium, Dulbecco's modified Eagle's Medium (DMEM), CELL-GRO FREE, DMEM/F12, advanced DMEM, DMEM/MCDB201, or Eagle's basal medium. The medium comprises 2-15% (v/v) serum. The medium comprises beta-mercaptoethanol. The medium comprises at least one antibiotic agent. The culture medium comprises glucose, L-valine, DMEM-low glucose, beta-mercaptoethanol, serum, and an antibiotic agent. The fragment of the placenta is a fragment of the neonatal or maternal aspect of the placenta. The method further comprises cryopreserving the placenta-derived cell; banking the placenta-derived cell; and expanding the selected cells on an uncoated or coated surface. The surface is coated with at least one of gelatin, collagen, fibronectin, laminin, ornithine, vitronectin, or extracellular membrane protein. In producing a population of placenta-derived cells, the expanding comprises culturing the cell in RPMI1640, Ham's F10 medium, Ham's F12 medium, Mesenchymal Stem Cell Growth Media, Iscove's modified Dulbecco's medium, Dulbecco's Modified Eagle's Medium (DMEM)-high glucose, DMEM-low glucose, advanced DMEM, DMEM/MCDB201, CELL-GRO FREE, DMEM/F12, or Eagle's basal medium. The expanding comprises further comprises culturing the cell in culture medium comprising DMEM-low glucose, serum, beta-mercaptoethanol, and an antibiotic agent. Preferred Kit: The kit comprises the cell that is cryopreserved or seeded on the scaffold. ACTIVITY - Vulnerary. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The cells are useful for treating patients requiring the repair or replacement of a tissue or organ resulting from disease or trauma or failure of tissue to develop normally, or to provide a cosmetic function, such as to augment the features of the body. ADMINISTRATION - Administration is oral, nasal, intraarterial, parenteral, intravenous, ophthalmic, intramuscular, subcutaneous, intraperitoneal, intracerebral, intraventricular, intracerebroventricul ar, intrathecal, intracisternal, intraspinal, or peri-spinal. No dosage is given. EXAMPLE - Placental tissue was obtained from National Disease Research Interchange (NDRI). The tissues were obtained from a pregnancy at the time of a normal surgical delivery. Placental cells were isolated aseptically in a laminar flow hood. (172 pages)

2/7/81 (Item 12 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0359163 DBR Accession No.: 2005-04867 PATENT
New isolated postpartum-derived cell capable of self-renewal and expansion in culture and having the potential to differentiate into a cell of cardiomyocyte phenotypes, useful for treating cardiomyopathy - for use in dilated, hypertrophic or restrictive cardiomyopathy therapy
AUTHOR: HARRIS I R; HARMON A M; KIHM A J; MESSINA D J; MISTRY S; SEYDA A; YI C; GOSIEWSKA A
PATENT ASSIGNEE: ETHICON INC 2005
PATENT NUMBER: WO 200501080 PATENT DATE: 20050106 WPI ACCESSION NO.: 2005-075564 (200508)
PRIORITY APPLIC. NO.: US 483264 APPLIC. DATE: 20030627
NATIONAL APPLIC. NO.: WO 2004US20957 APPLIC. DATE: 20040625
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated postpartum-derived cell comprising an L-valine-requiring cell derived from human postpartum tissue substantially free of blood, where the cell is capable of self-renewal and expansion in culture and having the potential to differentiate into a cell of cardiomyocyte phenotypes, and capable of growth in an atmosphere containing oxygen from 5-20%, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a population of cells comprising the postpartum-derived cell; (2) a cell lysate prepared from the population; (3) a therapeutic cell composition comprising a pharmaceutically-acceptable carrier and the post-partum-derived cells; (4) treating a patient with a disease of the heart or circulatory system by administering the therapeutic cell composition; (5) treating a patient with a cardiomyopathy comprising administering a therapeutic postpartum-derived cell composition to a patient with a cardiomyopathy; and evaluating the patient for improvements in cardiac function; and (6) a co-culture of human postpartum cells and another mammalian cell, where at least one of the cells is a cardiomyoblast, angioblast, or hemangioblast or induced to differentiate along a pathway leading to a cardiomyoblast, angioblast or hemangioblast.. BIOTECHNOLOGY - Preferred Cell: The isolated postpartum-derived cell comprises at least one of the following characteristics: (a) potential for at least about 40 doublings in culture; (b) attachment and expansion on a coated or uncoated tissue culture vessel, wherein a coated tissue culture vessel comprises a coating of gelatin, laminin, collagen, polyornithine, vitronectin, or fibronectin; (c) production of at least one of tissue factor, vimentin, and alpha-smooth muscle actin; (d) production of at least one of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, PD-L2 and HLA-A5B5C; (e) lack of production of at least one of CD31, CD34, CD45, CD80, CD86, CD117, CD141, CD178, B7-H2, HLA-G, and HLA-DR3DP5DQ, as detected by flow cytometry; (f) expression of at least one of interleukin 8; reticulon 1; chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha); chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2); chemokine (C-X-C motif) ligand 3; and tumor necrosis factor, alpha-induced protein 3; (g) expression of at least one of C-type (calcium dependent, carbohydrate-recognition domain) lectin, superfamily member 2 (activation-induced); Wilms tumor 1; aldehyde dehydrogenase 1 family, member A2; and renin; oxidized low density lipoprotein (lectin-like) %receptor% 1 ; Homo sapiens, clone IMAGE:4179671, mRNA, partial cds; protein ldnase C, zeta; hypothetical protein DKFZp564F013; downregulated in ovarian cancer 1; Homo sapiens mRNA; and cDNA DKFZp547K1113 (from clone DKFZp547K1113); (h) expression, which relative to a human cell that is a fibroblast, a mesenchymal stem cell, or an ileac crest %bone% marrow cell, is reduced for at least one of: short stature homeobox 2; heat shock 27kDa protein 2; chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1); elastin (supravalvular aortic stenosis, Williams-Beuren syndrome); Homo sapiens mRNA; cDNA DKFZp586M2O22 (from clone DKFZp586M2022); mesenchyme homeobox 2 (growth arrest-specific homeobox); sine oculis homeobox homolog I (Drosophila); crystallin, alpha B; disheveled associated activator of morphogenesis 2; DKFZP586B2420 protein; similar to neuralin 1; tetranectin (plasminogen %binding% protein); src homology three (SH3) and cysteine rich domain; B-cell translocation gene 1, anti-proliferative; cholesterol 25-hydroxylase; rant-related transcription factor 3; hypothetical protein FLJ23191; %interleukin% %11% %receptor%, alpha; procollagen C-endopeptidase enhancer; frizzled homolog 7 (Drosophila); hypothetical gene BC008967; collagen, type VIII, alpha 1; tenascin C (hexabrachion); iroquois homeobox protein 5; hephaestin; integrin, beta 8; synaptic vesicle glycoprotein 2; Homo

sapiens cDNA FLJ1 2280 fis, clone MAMMA1 001744; cytokine %receptor% -like factor 1; potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4; integrin, alpha 7; DKFZP586L151 protein; transcriptional co-activator with PDZ-%binding% motif (TAZ); sine oculis homeobox homolog 2 (Drosophila); KIAA1034 protein; early growth response 3; distal-less homeobox 5; hypothetical protein FLJ20373; aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); biglycan; fibronectin 1; proenkephalin; integrin, beta-like 1 (with EGF-like repeat domains); Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 1968422; EphA3; KIAA0367 protein; natriuretic %peptide% %receptor% C/guanylate cyclase C (atrionatriuretic %peptide% %receptor% C); hypothetical protein FLJ14054; Homo sapiens mRNA; cDNA. DKFZp564B222 (from clone DKFZp564B222); vesicle-associated membrane protein 5 (myobrevin); EGF-containing fibulin-like extracellular matrix protein 1; BCL2/adenovirus E1B 19kDa interacting protein 3-like; AE %binding% protein 1; cytochrome c oxidase subunit Vila %polypeptide% 1 (muscle); neuroblastoma, suppression of tumorigenicity 1; insulin-like growth factor %binding% protein 2, 36kDa; (i) secretion of at least one of MCP-I, IL-6, IL-8, GCP-2, HGF, KGF, FGF, HB-EGF, BDNF, TPO, MIP1a, RANTES, and TIMP1; and (j) lack of secretion of at least one of TGF-beta2, ANG2, PDGFbb, MFPIb, 1309, MDC, and VEGF, as detected by ELISA. The postpartum-derived cell is isolated in the presence of one or more enzyme activities comprising metalloprotease activity, mucolytic activity and neutral protease activity. The enzyme activities are collagenase and dispase. The cell further comprises hyaluronidase. It comprises a normal karyotype. The postpartum-derived cell maintains its karyotype as it is passaged. The cell expresses each of CD10, CD13, CD44, CD73, CD90, PDGFr-alpha, and HLA-A5B5C. The cell does not express any of CD31, CD34, CD45, CD117, CD 141, or HLA-DR5DP5DQ, as detected by flow cytometry. The cell does not spontaneously differentiate along a cardiogenic, angiogenic, hemangiogenic, or vasculogenic pathway when cultured in Growth Medium. Preferred Population: The population of cells comprises 1% postpartum-derived cells to 10% postpartum cells. It comprises 50 or 90% postpartum-derived cells. The population comprises substantially only postpartum-derived cells. The population comprises a clonal cell line of postpartum-derived cells. The population is incubated in the presence of one or more factors, which stimulate stem cell differentiation along a cardiogenic, angiogenic, hemangiogenic, or vasculogenic pathway. The factors comprise at least one of a demethylation agent, a member of BMP, FGF, TAK, GATA, Csx, NK, MEF2, ET-I, and Wnt factor families, Hedgehog, Csx/Nkx-2.5, and anti-Wnt factors. The demethylation agent comprises an inhibitor of DKA methyltransferase or inhibitors of a histone deacetylase, or inhibitors of a represser complex. The demethylation agents comprise at least one of 5-azacytidine, 5-aza-2'-deoxycytidine, DMSO, chelerythrine chloride, retinoic acid or their salts, 2-amino-4-(ethylthio)butyric acid, procainamide, and procaine. The population is seed onto a matrix to form a matrix-cell complex. The matrix is a scaffold that is bioabsorbable. The scaffold comprises at least one other cell type. The other cell type is a stem cell. Preferred Method: In the treatment methods, the patient has a cardiomyopathy, which can be idiopathic, ischemic or non-ischemic cardiomyopathy. The non-ischemic cardiomyopathy is selected from dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy. The cells are induced along a cardiogenic, angiogenic, hemangiogenic, or vasculogenic pathway. The method comprises cells induced in vitro, or cells that stimulate adult stem cells present in the heart to divide, or differentiate, or both. The administering is by injection. The injection is intracardiac injection. The cells are provided as a matrix-cell complex. The matrix is a scaffold that is bioabsorbable. Treating a patient with a disease of the heart or circulatory system alternatively comprises administering to the patient a therapeutic composition comprising one or more of postpartum-derived cells, a conditioned medium generated by postpartum-derived cells, a cell lysate derived from postpartum-derived cells, a %soluble% cell fraction from postpartum-derived cells, an extracellular matrix from postpartum-derived cells. The method further comprises co-administering one or more of an antithrombogenic agent, an anti-inflammatory, an immunosuppressive agent, an immunomodulatory agent, and an antiapoptotic agent. In treating a patient with a cardiomyopathy, the cells are induced along a cardiogenic, angiogenic, hemangiogenic, or vasculogenic pathway. The cells stimulate adult stem cells present in the heart to divide or differentiate, or both. The improvements include improvements in chest cardiac output (CO), cardiac index (CI), pulmonary artery wedge pressures (PAWP), and cardiac index (CI), % fractional shortening (%FS), ejection fraction (EF), left ventricular ejection fraction (LVEF); left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), contractility (e.g. dP/dt), pressure-volume loops, measurements of cardiac work, as well as an increase in atrial or ventricular functioning; an increase in pumping efficiency, a decrease in the rate of loss of pumping efficiency, a decrease in loss of hemodynamic functioning; and a decrease in complications associated with cardiomyopathy. The administering is in vivo by transplanting, implanting, injecting, fusing, delivering via catheter, or providing as a matrix-cell complex. The administering is by intracardiac injection. The administering is to a patient who is syngeneic with the postpartum-derived cells, or allogeneic. Preferred Composition: The therapeutic cell composition comprises a substantially homogeneous population of postpartum-derived cells. The therapeutic cell composition comprises a clonal cell line of postpartum-derived cells. The substantially homogeneous population is umbilical-derived cells. The substantially homogeneous population is substantially free of maternal cells. The substantially homogeneous population is placental-derived cells, or of neonatal or maternal origin. ACTIVITY - Cardiovascular-Gen.; Cardiant; Vasotropic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The cell, cell population and compositions are useful for treating cardiomyopathy, which can be idiopathic, ischemic or non-ischemic cardiomyopathy. The non-ischemic cardiomyopathy is selected from dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy (all claimed). ADMINISTRATION - Administration is by intracardiac injection (claimed). No dosage is given. EXAMPLE - Cells were isolated from cord blood samples. Samples of umbilical cord blood were mixed with lysis buffer. Cells were lysed at a ration of 1:20 cord blood to lysis buffer. The resulting cell suspension was vortexed for 5 seconds, and incubated for 2 minutes at ambient temperature. The lysate was centrifuged. The cell pellet was resuspended in complete minimal essential medium containing 10 percent fetal bovine serum, 4 millimolar glutamine, 100 units penicillin per 100 millimeters and 100 micrograms streptomycin per 100 millimeters. The resuspended cells were centrifuged, the supernatant was aspirated, and the cell pellet was washed in complete medium. Cells were seeded directly into T75 flasks, T75 laminin-coated flasks, or T175 fibronectin-coated flasks. (119 pages)

2/7/82 (Item 13 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0326273 DBR Accession No.: 2003-27414 PATENT
Producing neutrophils in vitro comprises culturing neutrophil progenitor cells with stromal cells to produce secondary differentiation culture which is cultured with stromal cells to produce functionally mature neutrophils - neutrophil production using embryonic stem cell and stromal cell culture and gene transfer and expression for neutropenia and leukemia therapy
AUTHOR: LIEBER J G; WORTHEN G S; WEBB S; KELLER G M
PATENT ASSIGNEE: NAT JEWISH MEDICAL and RES CENT 2003
PATENT NUMBER: WO 200380806 PATENT DATE: 20031002 WPI ACCESSION NO.: 2003-779253 (200373)
PRIORITY APPLIC. NO.: US 365440 APPLIC. DATE: 20020318
NATIONAL APPLIC. NO.: WO 2003US8840 APPLIC. DATE: 20030318
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Producing (M1) neutrophils in vitro comprising culturing an expanded population of neutrophil progenitor cells with semi-confluent stromal cells (I) in a medium suitable for animal cell culture comprising interleukin-6 (IL-6) family cytokine to produce secondary differentiation culture (II) and culturing cells from

(II) with (I) in a medium to produce functionally mature neutrophils, is new. DETAILED DESCRIPTION - Producing (M1) neutrophils in vitro comprises culturing an expanded population of neutrophil progenitor cells with semi-confluent stromal cells (I) in a medium suitable for animal cell culture comprising interleukin-6 (IL-6) family cytokine to produce secondary differentiation culture (II) and culturing cells from (II) with (I) in a medium suitable for animal cell culture comprising granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF) and IL-6 family cytokine to produce functionally mature neutrophils. An INDEPENDENT CLAIM is also included for an isolated, genetically modified neutrophil produced by (M1). BIOTECHNOLOGY - Preferred Method: The expanded population of neutrophil progenitor cells (III) which are day 8 or day 9, preferably day 8 embryoid body (EB) hematopoietic precursor cells, are produced by culturing stem cells such as embryonic stem cells for 8-9 days in a liquid medium in the absence of stromal cells, suitable for animal cell culture. The medium comprises platelet-depleted or preselected animal serum, L-glutamine, a protein-free hybridoma medium, ascorbic acid and monothioglycerol (MTG) without leukemia inhibitory factor (LIF). (I) does not produce macrophage colony stimulating factor (M-CSF) and is cultured with an agent that binds to and blocks or inactivates M-CSF. The agent is a %soluble% %receptor% for M-CSF or an antibody that selectively binds to M-CSF. (IL-6) family cytokine comprises IL-6, %interleukin%-%11% (IL-11), oncostatin M (OSM) or LIF. The medium further comprises basic fibroblast growth factor (bFGF), or c-kit ligand (KL) supernatant, IL-6, IL-11, LIF, MTG, OSM, a base medium suitable for the culture of animal cells or myeloid cells, platelet-depleted or preselected animal serum, L-glutamine, 2-mercaptoethanol, folic acid, i inositol, and hydrocortisone such as 21-hemisuccinate sodium salt. Culturing is performed for 2-6 days, or 2-4 days or preferably 6 days. Culturing is performed for 5-15 days or at least 5 days. Culturing is performed at 30 degrees centigrade-37 degrees centigrade or 37 degrees centigrade or 33 degrees centigrade with 20 % oxygen, less than 20 % oxygen, less than 10 % oxygen or preferably 5 % oxygen. (M1) further comprises an additional replating (M2) step between which involves harvesting cells in suspension, de-adhering (I) and adherent hematopoietic precursors, replating the de-adhered (I) and the obtained de-adhered adherent hematopoietic precursors on tissue culture plates for 20-45 minutes and adding cells that remained in suspension after replating, to the harvested cells. (M2) is carried out at 24 hours after beginning the culturing step. An additional step is also included in (M1) after performing the culturing step for at least 5-7 days. The step involves adding (III) and cells from (II) to the culture to provide an extended production of functionally mature neutrophils by (M1). Preferred Cells: The stem cells are embryonic stem cells. (III) is genetically modified. The genetic modification comprises transfection of stem cells which are genetically modified by deletion or inactivation of a gene in the cells to increase or initiate the expression of a gene in the cells, with a recombinant nucleic acid molecule encoding a heterologous protein. ACTIVITY - Cytostatic; Immunostimulant. No biological data given. MECHANISM OF ACTION - None given. USE - (M1) is useful for producing neutrophils in vitro. The neutrophils produced by (M1) are useful for increasing the number of neutrophils in a patient having neutropenia, leukemia, where the patient's endogenous neutrophils are functionally defective, impaired neutrophil function such as neutrophil granule deficiency, impaired neutrophil migration and a neutrophil %receptor% deficiency by administering the neutrophils to the patient. The neutrophils are also useful for regulating neutrophil activity in a patient (claimed). The neutrophils produced by (M1) are useful for reconstitution of neutrophils during %bone% narrow transplantation and for resolving overt and more subtle phenotypic abnormalities. (M1) is useful as an excellent model for studying neutrophil development, maturation and function, and role of neutrophils in inflammatory disease. ADMINISTRATION - The neutrophil is administered by intravenous, intraperitoneal, intramuscular, intranodal, intracoronary, intraarterial, subcutaneous, transdermal delivery, intratracheal, intraventricular, intraspinal, and pulmonary routes, and also by impregnation of a catheter, and direct injection into a tissue. The dosage is 0.5x10 to the power of 6 to 5.5x10 to the power of 10 neutrophils per individual per administration, and preferably 1x10 to the power of 8 to 5.5x10 to the power of 10 neutrophils. ADVANTAGE - (M1) enables an effective and sustained production of significant numbers of relatively pure, morphologically and functionally mature neutrophils. EXAMPLE - Embryonic stem cells (ES) were plated at a concentration of 800 - 1000 cells/ml into a non-treated Petri dish containing 5 ml of primary differentiation medium. The primary differentiation medium contained Iscove's modified dulbecco's medium (IMDM), 15 % pretested heat inactivated fetal calf serum (FCS), 2 mM L-glutamine, 4.5x10-4 M monothioglycerol (MTG), 50 microgram/ml of ascorbic acid, 5 % protein free hybridoma medium, 78 % by volume IMDM and 100 U/ml penicillin and 100 microgram/ml streptomycin. After primary differentiation for 8 days, the embryoid bodies (EBs) were trypsinized for 5 minutes at room temperature and disaggregated into a cell suspension. The cells were washed in 20 ml of IMDM and MTG containing 10 % fetal bovine serum (FBS), centrifuged and resuspended in gp-130 secondary differentiation medium and plated onto semiconfluent OP9 cells. Semi-confluent OP9 cells were utilized, as the fully confluent OP9 stromal cells were more likely to detach. The gp-130 secondary differentiation medium contained 10 % pretested heat inactivated FBS, 10 % horse serum, 5 % protein free hybridoma medium, 25 ng/ml oncostatin M (OSM), 10 ng/ml basic fibroblast growth factor (bFGF), 5 ng/ml interleukin-6 (IL-6), 1 % c-kit ligand supernatant (KL supernatant), 5 ng/ml %interleukin%-%11% (IL-11), and 1 ng/ml of recombinant leukemia inhibitory factor (LIF) in 79 % by volume IMDM containing 100 U/ml penicillin and 100 microgram/ml streptomycin and 1.5x10-4 M MTG. After 3 days in the gp-130 secondary differentiation medium, cells were transferred onto a semi-confluent OP9 monolayer at a concentration of approximately 4x10 to the power of 5 cells/ml containing a tertiary neutrophil differentiation medium containing 10 % platelet-depleted serum, 2 mM L-glutamine, 88 % by volume IMDM, 100 U/ml penicillin, 100 microgram/ml streptomycin, 1.5x10-4M MTG, 60 ng/ml granulocyte colony stimulating factor (G-CSF), 3 ng/ml granulocyte macrophage colony stimulating factor (GM-CSF) and 5 ng/ml IL-6. After four to twenty days, the cells were harvested for assays. For assessing the overall number and percentage of neutrophils produced, the wells containing differentiating neutrophils were harvested, cytospun, counted in a hemacytometer and stained with a Hema 3 staining kit. The percentage of mature neutrophils was morphologically assessed, and the number of neutrophils was determined from the total number of cells counted using a hemacytometer. To evaluate the relative maturity of the cells superficially associated with the OP9 stroma, cells associated with the neutrophil generating regions were aseptically harvested by fine needle aspiration under a dissecting microscope, cytospun, and the relative number and percentage of neutrophils were detected based on morphology. The result showed that by utilizing OP9 stromal cells the neutrophil production was enhanced from 5 to 10 fold compared to cultures without stroma. From 80000 pluripotent ES cells, approximately 6x10 to the power of 6 neutrophils were obtained for 7-14 days. The peak neutrophil production approached 8x10 to the power of 5 cells/well. OP9 cells markedly enhanced the percentage of mature neutrophils produced during the in vitro differentiation of ES cells into neutrophils. During peak periods of neutrophil production, which was maintained for at least a week, 75 to 96 % of the cells appeared to be neutrophils, with the majority of the cells being matured neutrophils. (60 pages)

2/7/83 (Item 14 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0319156 DBR Accession No.: 2003-20296 PATENT
New fusion partner cell comprising at least 2 ectopically expressed nucleic acid molecules, useful for diagnosing or treating cancer or infectious disease - primary mammal cell and partner cell fusion for hybridoma construction, monoclonal antibody preparation and gene therapy
AUTHOR: DESSAIN S; WEINBERG R
PATENT ASSIGNEE: WHITEHEAD INST BIOMEDICAL RES 2003
PATENT NUMBER: WO 200352082 PATENT DATE: 20030626 WPI ACCESSION NO.:

2003-533021 (200350)
PRIORITY APPLIC. NO.: US 375236 APPLIC. DATE: 20020424
NATIONAL APPLIC. NO.: WO 2002US40813 APPLIC. DATE: 20021218
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A fusion partner cell comprising at least 2 ectopically expressed nucleic acid molecules, is new. Each of the ectopically expressed nucleic acid molecules encodes a %polypeptide% that when expressed in the hybrid cell, alters the phenotype of the hybrid cell. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a hybridoma comprising the fusion partner cell fused to a primary mammalian cell; (2) an antibody producing cell, comprising the fusion cell fused to a B lymphocyte; (3) a method for making the fusion partner cell; (4) a method of making immunoglobulin-secreting hybrid cells; (5) a library of immunoglobulin-secreting cells comprising hybrid cells produced; (6) a method of making immunoglobulin-secreting cells; (7) an isolated immunoglobulin molecule; (8) a method of treating an infectious disease; (9) a method of treating cancer; (10) a method of diagnosing cancer; (11) a method of identifying novel tumor antigens; (12) cloning immunoglobulin-encoding nucleotide sequences; (13) a method of producing an antibody with a desired specificity; and (14) a method of identifying an antibody developed in a human in response to exposure of the immune system of the human to an antigen. BIOTECHNOLOGY - Preferred Cell: The fusion partner cell comprises a soluble or membrane bound growth factor comprises IL-6 and at least 1 ectopically expressed nucleic acid molecule that encodes at least 1 %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell or that encodes a growth promoting %polypeptide%. The nucleic acid is derived from a different species than the cell, or from a human. The nucleic acid encodes non-murine interleukin-6 (IL-6). The ectopically expressed nucleic acid molecule encodes a %polypeptide% that inhibits tumor suppressor activity. The %polypeptide% when expressed in the hybrid cell alters the phenotype of the hybrid cell comprises a %polypeptide% that inhibits tumor suppressor activity, a %polypeptide% that inhibits apoptosis, a %polypeptide% that promotes growth, or a %polypeptide% that enhances cell survival. At least 1 of the 2 %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell is a %polypeptide% that inhibits apoptosis. The %polypeptide% that inhibits apoptosis is a %polypeptide% that enhances telomerase activity. The %polypeptide% is a telomerase. The telomerase is the human telomerase catalytic subunit (hTERT). The %polypeptide% that inhibits apoptosis comprises bcl-2 or bcl-xL. 1 of the at least 2 %polypeptides% that when expressed in the hybrid cell alters the phenotype of the hybrid cell is a %polypeptide% that promotes growth. It comprises interleukin-6 (IL-6), %interleukin%-%11% (IL-11) v-Abl, c-myc or myb. IL-6 is human IL-6. 1 of the at least 2 %polypeptides% that when expressed in the hybrid cell alters the phenotype of the hybrid cell is a %polypeptide% that inhibits tumor suppressor activity. It is a %polypeptide% that inhibits p53 activity. It comprises p53 dominant negative proteins, SV40 large T antigen, HPV E6, mdm2, or Hdm2. The p53 dominant negative protein is a truncated p53 protein. The truncated p53 protein is a C-terminal p53 miniprotein (p53 DD). The %polypeptide% that inhibits tumor suppressor activity is a %polypeptide% that inhibits Rb activity. It comprises Rb dominant negative proteins, SV40 large T antigen, HPV E7, E1a, cdk/cyclin D fusion, IL-6 or mutant cdk4. 1 of the at least 2 %polypeptides% that when expressed in the hybrid cell alters the phenotype of the hybrid cell is a %polypeptide% that enhances cell survival. It enhances cell survival is SV40 small T antigen. The cell is a mammalian cell. It is a human cell, a mouse cell or a myeloma cell. The at least 2 ectopically expressed nucleic acid molecules are expressed from 1 or more exogenously introduced expression cassettes. The cassettes are included in viral or plasmid vectors. The vectors are or are not integrated in 1 or more chromosomes. Each cassette comprises at least 1 constitutive promoter operably linked to a nucleic acid molecule and at least 1 regulatable promoter operably linked to a nucleic acid molecule. The ectopically expressed nucleic acid molecules are antisense molecules that inhibit the expression of the %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell, or dsRNA molecules that inhibit the expression of the %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell. The ectopically expressed nucleic acid molecule encodes a molecule that modulates the expression of a %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell. The soluble growth factor is IL-6 or a mutant IL-6. Preferred Hybridoma: The hybridoma comprises the fusion partner cell fused to a primary mammalian cell. The primary mammalian cell and the fusion partner cell are derived from different species. The primary mammalian cell is a B lymphocyte. The fusion partner cell is a JB fusion partner cell. The primary mammalian cell comprises a tumor cell a hematopoietic cell, a lymphocyte, a T lymphocyte, a human cell, or a somatic cell. The B lymphocyte is obtained from tissue comprising peripheral blood, %bone% marrow, cord blood, lymph, nodes, Peyer's patches, spleen, tumor samples, or sites of infection. Preferred Immunoglobulin: The immunoglobulin molecule comprises an antigen-%binding% fragment or its CDR. It further comprises a detectable or toxic moiety, or a radionuclide. The detectable moiety comprises radionuclide, an enzyme, a fluorophore or a chromophore. The radionuclide comprises 225Ac, 211At, 212Bi, 213Bi, 186Rh, 188Rh, 177Lu, 90Y, 131I, 67Cu, 125I, 123I, or 77Br. The toxic moiety is a toxin. The toxin comprises enediynes, such as calicheamicin and esperamicin and chemical toxins such as methotrexate, doxorubicin, melphalan, chlorambucil, ARA-C, vindesine, mitomycin C, cis-platinum, etoposide, bleomycin or 5-fluorouracil. The antigen-%binding% fragment comprises Fab fragments, F(ab')2 fragments, Fd fragments, Fv fragments, dAb fragments or isolated CDRs. Preferred Method: Treating an infectious disease comprises administering the isolated immunoglobulin or its antigen-%binding% fragment or CDR region, where the infectious disease is caused by the infectious agent, and where the isolated immunoglobulin binds the infectious agent or an antigen. Treating cancer comprises administering the isolated immunoglobulin or its antigen-%binding% fragment or CDR region. Diagnosing cancer comprises administering to an individual suspected of having a tumor the isolated immunoglobulin molecule, or its antigen-%binding% fragment or CDR region, where the immunoglobulin, fragment or CDR region is detectably labeled, and where the isolated immunoglobulin binds the tumor or an antigen. The method also comprises: (a) obtaining a biological sample from an individual suspected of having a tumor, (b) contacting the biological sample with the isolated immunoglobulin molecule an antigen-%binding% fragment or a CDR region; or (c) determining the presence of the antigen recognized by the immunoglobulin, fragment or CDR region. Identifying novel tumor antigens comprises antigen-%binding% fragment or a CDR region, and identifying an epitope which binds to the immunoglobulin molecule, an antigen-%binding% fragment or a CDR region, where the epitope is a tumor antigen. Cloning immunoglobulin-encoding nucleotide sequences comprises: (a) preparing a library of human hybridoma cells; (b) selecting from the library 1 or more immunoglobulin-secreting cells of interest; and (c) isolating immunoglobulin-encoding nucleotide sequences from the selected immunoglobulin-secreting cells. Producing an antibody with a desired specificity comprises: (1) preparing a library of hybridoma pools; (2) performing limiting dilution on the hybridoma pools; (3) analyzing antibody produced by the hybridoma pools to identify a putative antibody with a desired specificity; (4) cloning immunoglobulin genes from hybridoma pools that produce the putative antibody; and (5) expressing the immunoglobulin genes in a host cell to produce an antibody with desired specificity. The antibody is analyzed to determine a physical characteristic comprising affinity, idiotype, allotype, isotype or conformation. The immunoglobulin genes encode a CDR region and variable and framework regions. The method further comprises performing recombinant DNA techniques to a phenotype of the antibody having desired specificity and cloning the immunoglobulin genes encoding a CDR region into a vector containing generic heavy chain and light chain constant domains. The hybridoma pools are the libraries of secreted immunoglobulin secreting hybrid cells. Identifying an antibody developed in a human in response to exposure of the immune system of the human to an antigen comprises:(a) generating fused cells by mixing together (under fusing conditions) human B cells with culturable fusion partner cells; (b) detecting a subset of surviving fused cells which express an antibody that selectively binds the antigen; (c) isolating nucleotide sequence encoding at least the

CDRs of the antibody from the subset of surviving fused cells; (d) transfecting nucleotide sequences isolated in (3) into a culturable cell line to produce culturable cells expressing antibodies comprising the CDRs; and (e) screening culturable cells produced in (4) to detect an antibody comprising the CDRs which binds to the antigen to identify an antibody. The antigen is an antigen of a pathogenic organism, an antigen of a tumor or an autoimmune antigen. The culturable fusion partner cells are fusion partner cells. The subset of surviving fused cells which express an antibody that selectively binds the antigen is detected by immunoassay. The immunoassay is an Enzyme Linked Immunosorbant Assay (ELISA) assay. The nucleotide sequences are extracted by polymerase chain reaction. Making immunoglobulin-secreting hybrid cells comprises fusing B lymphocytes to the fusion partner cells to form hybrid cells to produce immunoglobulin secreting hybrid cells. The method further comprises cloning the hybrid cells, culturing the hybrid cells in a selective medium that selects the B lymphocytes and the fusion partner cells, and identifying immunoglobulin-secreting hybrid cells in the culture. The hybrid cells are cloned by limiting dilution. The B lymphocytes are obtained from a mammal, a mouse or a human, horse, cow, sheep, pig, goat, rat, or rabbit. The mouse expresses a non-mouse immunoglobulin-encoding nucleotide sequence. The non-mouse immunoglobulin-encoding nucleotide sequences are human immunoglobulin chromosomal loci or cow immunoglobulin chromosomal loci. The B lymphocyte and the fusion partner cells are derived from a different species. Making immunoglobulin-secreting cells comprises fusing B lymphocytes to the fusion partner cells to form hybrid cells and maintaining resulting hybrid cells under conditions appropriate for production of immunoglobulin molecules by hybrid cells where immunoglobulin molecules are produced by hybrid cells. The method further comprises isolating the immunoglobulin molecules from the culture medium. The B lymphocytes are obtained from an individual. The individual is a mammal, which is a human. The immune system of the human has been previously exposed to an infectious agent, tumor or an antigen. The infectious agent comprises viruses, bacteria, fungi or prions. The human has developed an immune response against a self-antigen and has received a %bone% marrow transplant. The mammal is a mouse. Production: Making the fusion partner cell comprises introducing into a cell a nucleic acid molecule that encodes a %polypeptide% that inhibits tumor suppressor activity or at least two ectopically expressed nucleic acid molecules, each of which encodes a %polypeptide% that when expressed in the hybrid cell alters the phenotype of the hybrid cell. The method also comprises culturing the cells in the presence of a soluble growth factor comprising IL-6 or IL-11. The nucleic acid molecule is operably linked to a promoter, which is constitutively active or regulatable. ACTIVITY - Antimicrobial; Cytostatic. No biological data given. MECHANISM OF ACTION - Cell therapy. USE - The fusion partner cell is useful for diagnosing or treating cancer or infectious disease (claimed). ADMINISTRATION - Dosage comprises 10-100000 microg/kg. The composition is administered via oral or parenteral route. EXAMPLE - No relevant examples given.(91 pages)

2/7/84 (Item 15 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0314988 DBR Accession No.: 2003-16128 PATENT
New isolated polynucleotide encoding human %interleukin%-%11% receptor, useful treating %bone% loss associated with e.g. osteoporosis and for diagnosing expression of %interleukin%-%11% and its receptor - recombinant protein production in mammal cell useful for disease therapy and diagnosis
AUTHOR: TOBIN J
PATENT ASSIGNEE: GENETICS INST INC 2003
PATENT NUMBER: US 6528281 PATENT DATE: 20030304 WPI ACCESSION NO.: 2003-391389 (200337)
PRIORITY APPLIC. NO.: US 663584 APPLIC. DATE: 19960614
NATIONAL APPLIC. NO.: US 663584 APPLIC. DATE: 19960614
LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - A new isolated polynucleotide (I) comprises: (a) a sequence from nucleotide 803-1999 of a fully defined sequence of 2456 base pairs, given in the specification; (b) a nucleotide sequence varying from the sequence of (a) as a result of degeneracy of the genetic code; or (c) an allelic variant of the sequence in (a). DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a host cell transformed with (I); (2) producing a human %interleukin% %11% receptor (IL-11R) protein comprising: (a) growing a culture of the host cell of (1) in a suitable culture medium; and (b) purifying the human IL-11R protein from the culture; (3) an isolated polynucleotide comprising a sequence capable of hybridizing under stringent conditions to (I); and (4) an isolated polynucleotide comprising a sequence encoding a %peptide% or protein. WIDER DISCLOSURE - Also disclosed as new are: (1) a composition comprising an antibody which reacts with human IL-11R protein; (2) identifying an inhibitor of IL-11 %binding% to human IL-11R; and (3) inhibiting %binding% of IL-11 to human IL-11R. BIOTECHNOLOGY - Isolation: (I) was isolated from a cDNA library generated from activated human peripheral mononuclear cells (PBMC). Preferred Nucleic Acid: (I) is operably linked to an expression control sequence, and further comprises nucleotides 734-1999, 1067-1828 or 1067-1999. (I) also encodes for a protein having a biological activity of the human IL-11 receptor, and comprises the nucleotide sequences 803-1999, 803-1828, 1907-1999, 734-1828, 734-1810, 734-1768; 734-1768 or 734-1705. The encoded %peptide% or protein of the isolated polynucleotide of (4) comprises: (a) a fully defined sequence of 422 amino acids, given in the specification; or (b) a sequence from amino acids 24-422, 24-365, 391-422, 112-422, 112-365, 24-359, 24-345 or 24-324 of the sequence of (a). Preferred Host Cell: The cell is a mammalian cell. ACTIVITY - Osteopathic. No biological data given. MECHANISM OF ACTION - IL-11R inhibitor. USE - The human IL-11R protein is useful for screening agents which are capable of %binding% to human IL-11 or interfere with the %binding% of IL-11 to IL-11R. (I) and human IL-11R can also be used as diagnostic agents for detecting the expression of IL-11 or IL-11R. IL-11R and its inhibitors are also useful for the treatment of %bone% loss associated with osteoporosis, multiple myeloma and hypogonadal conditions. IL-11R is also useful for immunizing animals to obtain polyclonal and monoclonal antibodies which react with IL-11R protein and which inhibit IL-11 %binding% to IL-11R. ADMINISTRATION - Dosage is 0.1 micrograms-100 mgrams of IL-11R per/kg body weight. Administration is by oral, topical, buccal, intramuscular, intraperitoneal, intravenous, subcutaneous, inhalation or transdermal routes. EXAMPLE - cDNA was generated from activated human peripheral mononuclear cell (PBMC) using the Superscript Choice System and cloned into the EcoR1 site of ZAPII. The resulting phage were used to infect E. coli strain BB4. One million phage were plated on 150 mm NZCYM plated at a density of 15000 pfu/plate. Plaques were transferred to duplicate Duralose nitrocellulose filters. Following alkali denaturation and heat fixation the filters were pre-hybridized in 5 x SSC, 5 x Denhardts, 0.1% SDS, and 50 microgram/ml yeast tRNA for 2 hours at 65degreesC. Plaques that hybridized to both probes were identified by autoradiography. Following the secondary screen plasmid DNA was isolated from the ZAPII plaques by excision using helper phage. The DNA sequence of the inserts was determined on an Applied Biosystems DNA sequencer. Clone phIL11R14-2 containing the polynucleotide having the sequence with 2456 bp was deposited with ATCC 69731. (35 pages)

2/7/85 (Item 16 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0307364 DBR Accession No.: 2003-09149 PATENT
New retroviral long terminal repeat comprising a lentiviral R region which lacks all or a portion of the TAR sequence, useful for achieving long-term gene expression or for transferring selected genes into non-dividing cells - retro virus or lenti virus vector-mediated gene transfer and expression in host cell for use in gene therapy
AUTHOR: LEBOULCH P; WESTERMAN K
PATENT ASSIGNEE: GENETIX PHARM INC 2002

PATENT NUMBER: WO 200287341 PATENT DATE: 20021107 WPI ACCESSION NO.: 2003-156684 (200315)
PRIORITY APPLIC. NO.: US 288042 APPLIC. DATE: 20010501
NATIONAL APPLIC. NO.: WO 2002US14139 APPLIC. DATE: 20020501
LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - A retroviral long terminal repeat (LTR) (I) comprising a lentiviral R region which lacks all or a portion of the TAR sequence, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a left (5') retroviral LTR (II) comprising three regions, U3, R and U5, where the U3 region comprises a promoter sequence, the R region comprises a combination of a portion of an R region from a non-lentiviral retrovirus, and a portion of an R region from a lentivirus which does not include the TAR sequence, and the U5 region comprises a lentiviral U5 region; (2) a right (3') retroviral LTR (III) comprising three regions, U3, R and P, where the U3 region comprises the att sequence from a lentiviral U3 region but lacks any sequences from the U3 region having promoter activity, the R region comprises a combination of a portion of an R region from a non-lentiviral retrovirus, and a portion of an R region from a lentivims which does not include the TAR sequence, and the P region comprises a polyadenylation sequence; (3) a hybrid retroviral LTR (IV) comprising all or a portion of the R region from a non-lentiviral retrovirus and all or a portion of the U3 region or the U5 region from a lentivirus; (4) an expression vector (V) comprising (I), (II) or (III); (5) a virion (VI) for use in gene therapy comprising the (V); (6) delivering (M1) a gene to a cell by contacting the cell with (VI); and (7) producing (M2) a lentivirus for use gene therapy comprising transfecting the expression vector into a packaging cell line containing the necessary envelope (env) and polymerase (pol) gene sequences to produce the lentivirus. BIOTECHNOLOGY - Preferred Sequence: The TAR sequence or its portion is replaced by a comparable portion of the R region from a non-lentiviral retrovirus, thus forming a hybrid R region, where lentivirus is selected from HIV, EIV, SIV and FIV, preferably HIV-1 or HIV-2. The non-lentiviral retrovirus is selected from MoMSV, MoMLV, MLV, Friend, MSCV, RSV and spumavirus. The lentivirus is HIV and the non-lentiviral retrovirus is MoMSV. The hybrid R region comprises a portion of the HIV R region having the sequence (S1) and a portion of the MoMSV R region comprising the sequence (S2). The hybrid R region comprises a nucleotide sequence consisting of 67 base pairs given in the specification. The LTR is a left (5') LTR and further comprises a promoter sequence upstream from the hybrid R region, where the promoter sequence comprises the MoMSV U3 region of a non-lentiviral retrovirus. The retroviral LTR further comprises a lentiviral U5 region downstream from the hybrid R region, where the U5 region is the HIV U5 region including the HIV att sequence. The LTR may be a right (3') LTR and further comprises a portion of a lentiviral U3 region upstream from the hybrid R region, where the portion includes the lentiviral U3 att sequence but lacks any promoter activity, or comprises the 3' end of the lentiviral U3 region up to and including the lentiviral U3 att sequence. The portion of the U3 region is from HIV and comprises the sequence (S3). The retroviral LTR further comprises a polyadenylation sequence downstream from the hybrid R region, where the polyadenylation sequence comprises the rabbit beta-globin gene polyadenylation sequence, and the sequence (S4). For the left (5') retroviral LTR, the U3, R and U5 regions comprise fully defined sequences of 450 base pairs, 67 and 84 base pairs, respectively, and left (5') retroviral LTR comprises a sequence of 601 base pairs defined in the specification. For the right (3') retroviral LTR, the U3 region comprises the HIV att sequence and has the nucleotide sequence (S5). The R region comprises a portion of the MoMSV R region, and a portion of the HIV R region lacking the TAR sequence, where the R region comprises a sequence of 67 base pairs given in the specification. The P region comprises the rabbit beta-globin gene polyadenylation sequence, and the nucleotide sequence (S6). The right (3') retroviral LTR comprises a nucleotide sequence consisting of 129 base pairs defined in the specification. Preferred Expression Vector: (V) is a SIN vector, and further comprises a polypurine tract upstream from the U3 region of the right (3') LTR, an RNA export element comprising the HIV Rev responsive element (RRE), and an exogenous gene which can be a marker gene comprising the green fluorescence protein (GFP) gene, a therapeutic gene, or a gene which encodes a protein promoting angiogenesis. The expression vector further comprises a promoter sequence upstream from the gene, where the promoter is selected from PGK, EF1 alpha and CMV promoter, and is the natural promoter associated with the gene. The expression vector further comprises an internal ribosome entry site (IRES) and all or a portion of a lentiviral GAG sequence. The gene is selected from genes encoding %soluble% Interleukin-1 alpha %Receptor% Type I or Type II, Interleukin-1 alpha %Receptor% Antagonist Protein (IRAP), Insulin-Like Growth Factor (IGF), Tissue Inhibitors of Matrix Metallo-Proteinases (TIMP)-1 ,-2,-3, or -4, %Bone% Morphogenic Protein (BMP)-2 and -7, Indian Hedgehog, Sox-9, Interleukin-4, Transforming Growth Factor (TGF) -beta, Superficial Zone Protein, Cartilage Growth and Differentiation Factors (CGDF), Bcl-2, %Soluble% Tumor Necrosis Factor (TNF) - alpha %Receptor% , Fibronectin and/or Fibronectin Fragments, Leukemia Inhibitory Factor (LIF), LIF binding protein (Lbase pairs), Interleukin-4, Interleukin-10, %Interleukin%-%11% , Interleukin-13, Hyaluronan Synthase, %soluble% TNF-alpha %receptors% 55 and 75, Insulin Growth Factor (IGF)-1, activators of plasminogen, urokinase plasminogen activator (uPA), parathyroid hormone-related protein (PTHrP), and platelet derived growth factor (PDGF)-AA, -AB or-BB. Preferred Method: In (M1), the cell is selected from an autologous cell, a %bone% marrow cell, a mesenchymal stem cell obtained from adipose tissue, a synovial fibroblast or a chondrocyte, a non-autologous cell (i.e., allogeneic or xenogenic) and a cell from a cell line or from primary cells derived from a human or animal source. The virion is contacted with the cell in vivo or ex vivo. In (M2), the envelope (env) gene is from a non-lentiviral virus so that the lentivirus is pseudotyped. ACTGCTTAAG CCTCAATAAA GCTTGCCTTG AGTGCTTCA (S1) GCGCCAGTCT TCCGATAGAC TGCGTCG (S2) CTGGAAGGGC TAATTCACTC CCAAAGAAGA CAAGATAT (S3) AGTTGTGTGT TGGTTTTTTG TGTG (S4) CTGGAAGGGC TAATTCACTC CCAAAGAAGA CAAGATAT (S5) ATGTGTGTGT TGGTTTTTTG TGTG (S6) ACTIVITY - None given. MECHANISM OF ACTION - Gene therapy. No biological data given. USE - The expression vector is useful in gene therapy (claimed). The LTR is useful in achieving long-term gene expression or for transferring selected genes into non-dividing cells including cells of the skin, gastrointestinal tissue, cardiac tissue, and neuronal tissue. ADMINISTRATION - No administration routes or dosage details given. ADVANTAGE - The lentiviral vectors are safer to prevent replication-competent virus, while maintaining sequences necessary for obtaining high viral titers capable of infecting a wide variety of dividing as well as non-dividing cells. EXAMPLE - A hybrid retroviral vector in which portions of the U3, R and/or U5 regions from the HIV long terminal repeat (LTR) were deleted or replaced by comparable portions of the LTR from MoMSV was constructed through a series of cloning steps combining pieces from several plasmids using standard cloning techniques. The 5' LTR (plasmid D) was constructed by combining pieces from plasmids A, B and C. The 3' LTR (plasmid E) was constructed by cloning a series of annealed oligonucleotides into plasmid A. The 5' LTR along with the piece of gag from plasmid D was cloned into plasmid E creating a plasmid which contained both the 5' and 3' LTRs. Other components such as the RRE, selection marker and cppt were then subcloned into the plasmid containing bothLTRs. The completed hybrid vector contained the following components (from left to right): (a) a hybrid 5' LTR, containing the MoMSV U3, the left half of the MoMSV R, the right half of the HIV R (without TAR) and the HIV U5; (b) the HIV packaging signal which is part of the sequence leading into the HIV GAG sequence; (c) the HIV GAG sequence; (d) the HIV central polypurine tract (cppt); (e) the HIV RRE (rev response element); (f) the GFP gene coupled downstream from the PGK promoter; and (g) a polypurine tract leading into a hybrid 3' LTR, including (from left to right) the HIV att sequence, the same hybrid MoMSV-HIV R as in the 5' LTR and the rabbit beta-globin polyadenylation sequence. Plasmid A was made by cloning annealed oligo OPLB 10/11 into Puc 19. Plasmid B, a piece of plasmid PLXSN, was subcloned into plasmid A, forming the MoMSV 5' LTR U3 region and the left portion of the MoMSV R region. Plasmid C was subcloned from HIVNL-43 and contained the HIV 5' LYR from the R region through the U5 region , and through the packaging signal at the start of GAG sequence. Plasmid D was formed by combining plasmids A, B and C to form the complete 5' hybrid LTR followed by the start of the HIV GAG sequence.

Plasmid E was constructed by cloning a series of annealed oligos into plasmid A. (55 pages)

2/7/86 (Item 17 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0306507 DBR Accession No.: 2003-08292 PATENT
Identifying biologically active agents comprises cloning transfected cells into a cell array, exposing the array to an agent to be tested, and detecting signals generated by a reporter molecule as a result of exposure to the agent - vector-mediated gene transfer and expression in host cell for high throughput screening
AUTHOR: ANDREWS P; DRAPER J; WALSH J
PATENT ASSIGNEE: AXORDIA LTD 2002
PATENT NUMBER: WO 200290992 PATENT DATE: 20021114 WPI ACCESSION NO.: 2003-120579 (200311)
PRIORITY APPLIC. NO.: GB 200111004 APPLIC. DATE: 20010504
NATIONAL APPLIC. NO.: WO 2002GB1946 APPLIC. DATE: 20020429
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Screening (M1) for identifying biologically active agents, comprises: (i) providing a population of cells stably transfected with a nucleic acid encoding a reporter molecule; (ii) cloning the transfected cells into a cell array; (iii) exposing the array to at least one agent to be tested; and (iv) detecting a signal generated by the reporter molecule as a result of exposure to the agent. DETAILED DESCRIPTION - Screening (M1)for identifying biologically active agents, comprises: (i) providing a population of cells which have been stably transfected with a nucleic acid molecule encoding a reporter molecule; (ii) cloning the transfected cells into a cell array; (iii) exposing the array to at least one agent to be tested; and (iv) detecting a signal generated by the reporter molecule as a result of exposure to the agent. INDEPENDENT CLAIMS are also included for the following: (1) An agent identified by M1; (2) A cell or a cell array obtained by M1; (3) Screening (M2) for the isolation of a gene, comprising: (a) steps (i)-(iv) of M1; (b) extracting nucleic acid from a cell sample comprising the cell array; and (c) determining the sequence of at least part of the genomic region into which the nucleic acid encoding the reporter molecule has integrated; (4) Comparing the biological activity of a reference agent with at least one other agent, comprising: (a) steps (i) and (ii) of the above method; (b) preparing a duplicate array; (c) step (iii) of the above method; (d) exposing the duplicate array to a reference agent; and (e) detecting a signal generated by the reporter molecule as a result of exposure to the agent and to the reference agent; and (5) A vector comprising a reporter molecule, a splice acceptor site and an internal ribosome entry site, where the splice acceptor and the internal ribosome entry site are operably linked to facilitate expression of the reporter molecule. BIOTECHNOLOGY - Preferred Methods: The methods of identifying biologically active agents and of comparing the biological activity of a reference agent with at least one other agent, further comprise: (a) collating the signal(s) generated by the reporter molecule; (b) converting the collated signal(s) into a data-analyzable form; and optionally (c) providing an output for the analyzed data. In identifying biologically active agents, the cells are eukaryotic or prokaryotic cells. The eukaryotic cells are protozoan, fungal, or mammalian cells. The protozoan cell is selected from Plasmodium spp , Plasmodium falciparum, Leishmania spp, Leishmania major, Trypanosoma brucei spp, Trypanosoma brucei brucei, Trypanosoma brucei rhodesiensis, Trypanosoma cruzii, Giardia spp, Cryptosporidium spp, Acanthamoeba spp, Babesia spp, Babesia bovis, Toxoplasma spp, Entamoeba spp,Naegleria spp. The fungal cell is selected from Saccharomyces cerevisiae, Candida spp and Candida albicans. The prokaryotic cell is selected from Staphylococcus aureus; and S. epidermidis, Enterococcus faecalis, Mycobacterium tuberculosis, M. bovis, M. leprae, Streptococcus group B, Streptococcus pneumoniae, Streptococcus equi, Streptococcus pyogenes, Streptococcus coelicor, Helicobacter pylori, Neisseria gonorrhea, Streptococcus group A, Borrelia burgdorferi, Coccidioides immitis, Histoplasma capsulatum, Neisseria meningitidis type B, Neisseria meningitidis type C, Shigella flexneri, Escherichia coli, Haemophilus influenzae, Bacteroides fragilis, Bordetella bronchiseptica, Bordetella parapertussis, Bordetella pertussis, Burkholderia pseudomallei, Campylobacter jejuni, Clostridium difficile, Corynebacterium diphtheria, Salmonella typhi, Yersinia enterocolitica andYersinia pestis. The mammalian cell is derived from a primary cell line selected from fibroblasts, keratinocytes, endothelial cells, renal tubular cells, neural cells, hepatocytes, or preferably, stem cells. The stem cell is preferably a human embryonic stem cell, but may also be a hematopoietic stem cell, neural stem cell, %bone% stem cell, muscle stem cell, embryonic germ cell, mesenchymal stem cell, trophoblastic stem cell, epithelial stem cell (derived from organs such as the skin, gastrointestinal mucosa, kidney, bladder, mammary glands, uterus, prostate, and endocrine glands such as the pituitary), endodermal stem cell (derived from organs such as the liver, pancreas, lung and blood vessels), or embryonal carcinoma cell. The agent is a %polypeptide% and is selected from frizzled related %polypeptides% (FRP), Wnt Inhibitory Factors (WIF), Dickkopf and Cerebrus. The %polypeptide% comprises a sequence selected from any of the 47 fully defined amino acid sequences given in the specification, or their active %binding% fragments. The agent may also be a double-stranded RNA derived from the nucleic acid molecules comprising any of the 51 fully defined nucleotide sequences given in the specification, or their fragments. In addition, the agent is selected from a growth hormone, leptin, erythropoietin, prolactin, tumor necrosis factor, interleukins (IL), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, ciliary neurotrophic factor, cardiotrophin-1, leukemia inhibitory factor, oncostatin M, interferon, interferon alpha or gamma, fibroblast growth factor family, the epidermal growth factor family, the %bone% morphogenic and T-cell growth factor beta super families, sonic hedgehog, indian hedgehog, desert hedgehog, and stem cell factor. The agent may also be an antisense nucleic acid or an aptamer. Alternatively, the agent is selected from retinoic acid, hexamethylene bisacetamide, bromodeoxyuridine, and lithium. Preferred Vector: The vector comprises a splice acceptor that is positioned 5' to an internal ribosome entry site. The vector includes a nucleic acid molecule which encodes a selectable marker or a green fluorescent protein reporter molecule. Preparation: The cell and the vector are prepared by standard recombinant techniques. USE - The method is useful in identifying biologically active agents and the genes through which the agents act, in screening potential drugs for their ability to activate certain drug targets in a high-throughput assay, in identifying relationships between signaling pathways and specific signals that could be useful in eventually directing the differentiation of embryonic stem cells, and in toxicology assays by testing for unwanted activation or inhibition of specific signaling pathways. The vector is useful in carrying out the above methods (claimed). EXAMPLE - No suitable example given.(90 pages)

2/7/87 (Item 18 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0305514 DBR Accession No.: 2003-07299 PATENT
Gene therapy for treating arthritis, e.g. osteoarthritis or rheumatoid arthritis, comprises administering a therapeutic gene using a lentiviral vector, or cells transfected with the therapeutic gene using the lentiviral vector - virus vector expression in human cell for use in disease gene therapy
AUTHOR: PAWLIUK R; LEBOULCH P
PATENT ASSIGNEE: GENETIX PHARM INC 2002
PATENT NUMBER: WO 200282908 PATENT DATE: 20021024 WPI ACCESSION NO.: 2003-067542 (200306)
PRIORITY APPLIC. NO.: US 284736 APPLIC. DATE: 20020319
NATIONAL APPLIC. NO.: WO 2002US8711 APPLIC. DATE: 20020321
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Treating arthritis comprises: (a)

delivering to a subject a therapeutic gene using a lentiviral gene delivery vector, so that the gene is expressed at sufficient levels and period to treat a patient; or (b) transfecting cells ex vivo with a therapeutic gene using a lentiviral gene delivery vector and administering the cells to the subject.BIOTECHNOLOGY - Preferred Vector: The lentiviral vector is HIV, FIV, SIV, BIV, or EIAV vectors. Preferred Genes: The therapeutic gene is %soluble% interleukin-1alpha %Receptor% Type I, %Soluble% Interleukin-1alpha %Receptor% Type II, Interleukin-1alpha %Receptor% Antagonist Protein (IRAP), Insulin-Like Growth Factor (IGF), Tissue Inhibitors of Matrix Metallo-Proteinases (TIMP)-1, -2, -3, -4, %Bone% Morphogenic Protein (BMP)-2 and -7, Indian Hedgehog, Sox-9, Interleukin-4, Transforming Growth Factor (TGF)-beta, Superficial Zone Protein, Cartilage Growth and Differentiation Factors (CGDF), Bcl-2, %Soluble% Tumor Necrosis Factor (TNF)-alpha %Receptor%, Fibronectin and/or Fibronectin Fragments, Leukemia Inhibitory Factor (LIF), LIF binding protein (LBP), Interleukin-4, Interleukin-10, %Interleukin%-%11%, Interleukin-13, Hyaluronan Synthase, %soluble% TNF-alpha %receptors% 55 and 75, Insulin Growth Factor)IGF)-1, activators of plasminogen, urokinase plasminogen activator (uPA), parathyroid hormone-related protein (PTHrP), or platelet derived growth factor (PDGF)-AA, -AB or -BB. Preferred Cells: The cells transfected with the therapeutic gene are autologous (e.g. %bone% marrow cells, mesenchymal stem cells obtained from adipose tissue, or synovial fibroblasts or chondrocytes), or non-autologous (e.g. a cell line or primary cells derived from a human or animal source). ACTIVITY - Antiarthritic. Knees were macroscopically observed for differences and improvements in arthritic rats injected with recombinant lentivirus. Arthritic knees injected with hIL-1Ra lentivirus showed reduced swelling in comparison to knees contralateral to the lentiviral injection. Histological analysis using toluidine blue revealed extreme cartilage damage in the arthritic knees. This damage was not observed in the arthritic knees injected with lentiviral hIL-1Ra. MECHANISM OF ACTION - Gene Therapy. USE - The method is useful in gene therapy, particularly for treating arthritis (claimed), e.g. osteoarthritis or rheumatoid arthritis. ADMINISTRATION - The lentiviral vector is injected directly into an affected joint of the subject (claimed). Administration may also be intravenous, intramuscular, topical, oral, or by gene gun or hypospray instrumentation. No dosage given. (54 pages)

2/7/88 (Item 19 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0301969 DBR Accession No.: 2003-03754 PATENT
Novel human %interleukin%-%11% receptor protein useful for inhibiting %binding% of %interleukin%-%11% to the human %interleukin%-%11% receptor, and for treating or preventing loss of %bone% mass in a mammalian subject - vector-mediated recombinant protein gene transfer and expression in host cell for disease therapy
AUTHOR: TOBIN J
PATENT ASSIGNEE: GENETICS INST INC 2002
PATENT NUMBER: US 20020082233 PATENT DATE: 20020627 WPI ACCESSION NO.: 2002-697273 (200275)
PRIORITY APPLIC. NO.: US 924338 APPLIC. DATE: 20010807
NATIONAL APPLIC. NO.: US 924338 APPLIC. DATE: 20010807
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated human %interleukin%-%11% receptor (IL-11R) protein (I) comprising an amino acid sequence selected from a fully defined sequence of 422 amino acids (S1) as given in the specification, a sequence comprising amino acids 24-422, 24-365, 391-422, 112-422, 112-365, 24-359, 24-345 or 24-324 of (S1) or fragments of the above with biological activity of the human IL-11R, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated polynucleotide (II) encoding (I) or comprising a nucleotide sequence selected from the sequence (S2) of 2456 bp fully defined in the specification, from nucleotide 803 to 1999 of (S2), a sequence varying from S2 as a result of degeneracy of the genetic code, a fragment of the above sequences encoding a protein having the ability to bind IL-11, or an allelic variant of S2; (2) a host cell (III) transformed with (II); (3) production of (I); (4) a protein produced by the above method; (5) a composition (IV) comprising an antibody which specifically reacts with (I); (6) an inhibitor (V) identified using (I); and (7) a pharmaceutical composition (VI) comprising (I) or (V) and a carrier. BIOTECHNOLOGY - Preparation - (I) is produced by growing a culture of mammalian cell in a suitable culture medium, and purifying the human IL-11R protein from the culture (claimed). Preferred %Polypeptide%: (I) comprises a sequence beginning at amino acid 26, 23 or 1 of (S1). Preferred Polynucleotide: (II) include a nucleotide encodes for a protein having a biological activity of the human IL-11 receptor and is operably linked to an expression control sequence. (II) comprises a sequence of (S1) from nucleotide 803-1999, 734-1999, 1067-1828, 1067-1999, 734-1828, 734-1810, 734-1768 or 734-1705, or from nucleotides 803-1828, 1907-1999 or its fragments. ACTIVITY - Osteopathic; Cytostatic; Antianemic; Antibacterial; Virucide; Immunostimulant. No supporting data given. MECHANISM OF ACTION - Inhibitor of IL-11 %binding% to human IL-11 receptor (claimed); Regulator of %bone% maturation and repair. No supporting data given. USE - (I) is useful for identifying an inhibitor of IL-11 %binding% to the human IL-11 receptor, by combining (I) with IL-11 (its fragment) to form a first %binding% mixture, measuring the amount of %binding% between (I) and IL-11, combining a compound with (I) and IL-11 to form a second %binding% mixture, measuring the amount of %binding% in the second %binding% mixture, and comparing the amount of %binding% in the first %binding% mixture with that of in the second %binding% mixture, where the compound is capable of inhibiting IL-11 %binding% to the human IL-11 receptor when a decrease in the amount of %binding% of the second %binding% mixture occurs. The first and second %binding% mixture comprise gp130 or its fragment capable of %binding% to (I) or IL-11. (IV) and (VI) are useful for inhibiting %binding% of IL-11 to the human IL-11 receptor, and for treating or preventing loss of %bone% mass in a mammalian subject (all claimed). (I) is useful for producing antibodies. (I) and (II) are useful as diagnostic agents for detecting the expression or presence of IL-11R, IL-11 or cells expressing them. (I) and (V) are useful for treating %bone% loss (i.e., associated with osteoporosis, post-menopausal osteoporosis, senile osteoporosis, idiopathic osteoporosis, Paget's disease, multiple myeloma, and hypogonadal conditions). (I) and (V) are also useful in treating or modulating Il-11 related conditions which include immune deficiencies specifically deficiencies in hematopoietic progenitor cells, or disorders relating to cancer and other diseases such as leukopenia, bacterial and viral infections, anemia, B cell or T cell deficiencies. ADMINISTRATION - Administered at a dose of 0.1 mug-100 mg/kg/body weight, by oral, inhalation, cutaneous, subcutaneous, or intravenous route. EXAMPLE - Isolation of human %interleukin%-%11% receptor (IL-11R) cDNA was as follows. DNA probes derived from the murine Et1-2 sequence (1714 bp) were obtained by polymerase chain reaction (PCR) from murine placenta cDNA. The amino terminal probe corresponded to base pairs 418-570 and the carboxy terminal probe to base pairs 847-1038 of the murine Et1-2 sequence. The DNA probes were gel purified and radiolabeled using alpha32P-dATP and alpha32P-dCTP. cDNA was generated from activated human peripheral blood mononuclear cells (PBMC) using the Superscript Choice System and cloned into the EcoRI site of ZAP II. The resulting phage were used to infect Escherichia coli strain BB4. One million phage were plated onto 150 mm NZCYM plates at density of 15000 plaque forming units (pfu)/plate. Plaques were transferred to duplicate Duralose nitrocellulose filters. Following alkali denaturation and heat fixation the filters were pre-hybridized in 5xSSC, 5xDenhardts, 0.1% sodium dodecyl sulfate (SDS), and 50 mug/ml yeast tRNA for 2 hours at 65degreesC. One set of filters was hybridized with the amino-terminal probe and the other set with the carboxy terminal probe for 48 hours at 55degreesC in pre-hybridization buffer. The filters were washed. Plaques that hybridized to both probes were identified by autoradiography. Of the one million plaques screened two plaques hybridized to both of the probes. These plaques were picked and the phage were eluted into SM media containing chloroform. The resulting phage were used to reinfect E.coli strain BB4 and plated on NZCYM plates at a density of 100-300 pfu/plate for a secondary screen. Following the secondary screen

plasmid DNA was isolated from the ZAPII plaques. The DNA sequence of the inserts was determined on an Applied Biosystems DNA sequencer. Clone phIL11R14-2 containing the polynucleotide having the sequence of 2456 bp fully defined in the specification was deposited with ATCC at accession number 69731. (22 pages)

2/7/89 (Item 20 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0290384 DBR Accession No.: 2002-12231 PATENT
Novel isolated human %interleukin%-%11% %receptor% protein useful in assays to screen for %binding% agents and for treating immune deficiencies, cancer and %bone% related disorders, e.g., osteoporosis - vector-mediated gene transfer and expression in host cell for recombinant protein production, drug screening and disease therapy
AUTHOR: TOBIN J
PATENT ASSIGNEE: GENETICS INST INC 2002
PATENT NUMBER: US 6350855 PATENT DATE: 20020226 WPI ACCESSION NO.: 2002-215268 (200227)
PRIORITY APPLIC. NO.: US 929846 APPLIC. DATE: 19970915
NATIONAL APPLIC. NO.: US 929846 APPLIC. DATE: 19970915
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated human %interleukin%-%11% %receptor% (IL-11R) protein (I), comprising a sequence selected from: (a) the fully defined 422 amino acid sequence (S1) as given in the specification; (b) residues 24-422 of (S1); (c) residues 24-365 of (S1); (d) residues 391-422 of (S1); (e) residues 112-422 of (S1); (f) residues 112-365 of (S1); (g) residues 24-359 of (S1); (h) residues 24-345 of (S1); and (i) residues 24-324 of (S1), is new. WIDER DISCLOSURE - Also disclosed as new are the following: (1) polynucleotides encoding (I); (2) host cells, preferably mammalian cells, transformed with the polynucleotides; (3) a process for producing (I); (4) compositions comprising an antibody which specifically reacts with (I); (5) identifying an inhibitor of IL-11 %binding% to the human IL-11 %receptor%; and (6) inhibiting %binding% of IL-11 to the human IL-11 %receptor% in a mammal. BIOTECHNOLOGY - Preparation: (I) may be prepared according to standard recombinant methodologies. Preferred %Polypeptides%: (I) may preferably comprise (S1) or any of (b)-(i) above. ACTIVITY - Immunomodulatory; cytostatic; osteopathic. No supporting data given. MECHANISM OF ACTION - %Interleukin%-%11% %receptor% involved in regulation of the immune system by interaction with IL-11; inhibitor of IL-11R. No supporting data given. USE - (I) may be used to screen for agents which are capable of %binding% to human IL-11R or interfere with the %binding% of IL-11 to the human IL-11R. In addition, (I) may also be used as diagnostic agents for detecting the expression or presence of IL-11R, IL-11 or cells expressing IL-11R or IL-11. (I) and IL-11R inhibitors may be useful in treatment or modulation of various medical conditions in which IL-11 is implicated or which are effected by the activity (or lack of) of IL-11 (collectively IL-11-related conditions). These conditions include immune deficiencies, specifically deficiencies in hematopoietic progenitor cells, or related disorders, cancer and other diseases. It is also believed that IL-11 and IL-11R may play a role in the regulation of %bone% maturation and repair (Girasole et al. (1994) J. Clin. Invest. 93, 1516-1524; Passeri et al. (1992) J. %Bone% Miner. Res., 7(S1), S110 Abst.; Passeri et al. (1993) J. %Bone% Miner. Res., 8(S1), S162 Abst.). As a result, human IL-11R protein and IL-11R inhibitors may be useful in treatment of %bone% loss (including that associated with osteoporosis, post-menopausal osteoporosis, senile osteoporosis, idiopathic osteoporosis, Pagets disease, multiple myeloma, and hypogonadal conditions). ADMINISTRATION - Administration is by oral ingestion, inhalation, or cutaneous, subcutaneous, or (preferably) intravenous injection. Dosage is 0.1microg-100 mg per kg body weight. EXAMPLE - DNA probes derived from the murine Etl-2 sequence (a fully defined 1714 nucleobase sequence (N1) given in the specification) were obtained by PCR from murine placenta cDNA. The amino terminal probe corresponds to base pairs 418-570 and the carboxy terminal probe to base pairs 847-1038 of the murine Etl-2 sequence. The DNA probes were gel purified and radiolabeled cDNA was generated from activated human peripheral blood mononuclear cells (PBMC) using the Superscript Choice System and cloned into the EcoR1 site of ZAP II (Stratagene). The resulting phage were used to infect E. coli strain BB4. Phage were plated on 150 mm NZCYM plates at a density of 15000 pfu/plate. Plaques were transferred to duplicate Duralose nitrocellulose filters (Stratagene). Following alkali denaturation and heat fixation the filters were pre-hybridized in 5x SSC, 5x Denhardts, 0.1% SDS, and 50 microg/ml yeast tRNA for 2 hours at 65degrees C. One set of filters was hybridized with the amino-terminal probe and the other set with the carboxy-terminal probe (5x105 cpm/ml) for 48 hrs at 55 degreesC in pre-hybridization buffer. The filters were washed with 4x SSC, 0.1% SDS once at 25degrees C and twice at 55 degreesC. Plaques that hybridized to both probes were identified by autoradiography. Two plaques hybridized to both of the probes. These plaques were picked and the phage eluted into SM media containing chloroform. The resulting phage were used to reinfect E. coli strain BB4 and plated on NZCYM plates at a density of 100-300 pfu/plate for a secondary screen. Following the secondary screen plasmid DNA was isolated from the ZAPII plaques by excision using helper phage (Stratagene). The DNA sequence of the inserts was determined on an Applied Biosystems DNA sequencer. Clone phIL11R14-2 containing the polynucleotide having the fully defined 2456 nucleobase sequence (N2) given in the specification was deposited with ATCC at accession number 69731 on Dec. 22, 1994. A portion of the full length human IL-11R sequence (nucleotides 734-1828 (N2) encoding amino acids 1-365 of the fully defined 422 amino acid sequence (S1) as given in the specification) corresponding to a %soluble% form was cloned into the mammalian expression vector pED and used to transfect COSM6 cells. 40 hours after transfection conditioned media was removed, concentrated 5 fold and used in proliferation assays with the murine cell line BAF130-9 (Hibi, M. et al. (1990) Cell 63, 1149-57), a derivative of the BAFB03 cell line expressing the human gp130 signal transducer. BAF130-9 cells do not proliferate in response to IL-11 or IL-6 alone, but do proliferate in response to a combination of IL-6 and %soluble% IL-6R (Hibi et al., supra). BAF130-9 cells (1x104 cell in 0.1 ml) were cultured in RPMI 1640 medium/10% FCS with increasing concentrations of recombinant human IL-11 in the absence or presence of 10 microl of conditioned media from mock transfected cells or cells transfected with the %soluble% human IL-11R sequence. After forty hours the cells were pulse-labeled with 3H-thymidine (0.5 microCi/well) for eight hours and incorporated nucleotide was determined. BAF130-9 cells do not proliferate in response to IL-11 or %soluble% IL-11R alone, but do proliferate in the presence of both IL-11 and %soluble% IL-11R. (75 pages)

2/7/90 (Item 21 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0183305 DBR Accession No.: 95-10126 PATENT
Proteins and %peptides% fused to thioredoxin or thioredoxin-like molecules - Escherichia coli and human thioredoxin and e.g. %interleukin%-%11% fusion protein production by plasmid expression in bacterium, for application in recombinant protein production
AUTHOR: McCoy J; Diblasio-Smith E; Grant K; Lavallie E R
PATENT ASSIGNEE: Genet.Inst.Cambridge-Massachusetts 1995
PATENT NUMBER: WO 9516044 PATENT DATE: 950615 WPI ACCESSION NO.: 95-224326 (9529)
PRIORITY APPLIC. NO.: US 165301 APPLIC. DATE: 931210
NATIONAL APPLIC. NO.: WO 94US14179 APPLIC. DATE: 941208
LANGUAGE: English
ABSTRACT: The following are claimed: (1) isolated DNA encoding a fusion protein composed of 1st and 2nd DNA sequences encoding 1st and 2nd proteins (the DNA sequence encodes at least 2 metal-%binding% amino acids); (2) plasmid DNA composed of a 1st DNA encoding 1 or more thioredoxin-like proteins fused to a 2nd DNA encoding a 2nd protein (the fusion sequence is under control of an expression control sequence composed of a promoter functional in Escherichia coli, a ribosome %binding% site, a replication origin, and an optionally selectable

marker); (3) a host cell transformed with the DNA; (4) a fusion protein composed of a thioredoxin-like protein fused to a nd protein; and (5) a method of purifying a protein or fusion protein. The fusion proteins retain the desirable characteristics of a thioredoxin-like protein, and allow %peptides% /proteins fused at the free ends of the thioredoxin-like protein to achieve its desired conformation. The DNA is useful for the production of large amounts of recombinant %peptides% or proteins in a stable, soluble form. The fusion proteins may be used therapeutically, or as a vehicle for the delivery of bioactive %peptides%. (75pp)

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